(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 August 2004 (12.08.2004)

PCT

(10) International Publication Number
WO 2004/067480 A2

(51) International Patent Classification[7]: C07C

(21) International Application Number:
PCT/GB2004/000238

(22) International Filing Date: 22 January 2004 (22.01.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0301872.8	25 January 2003 (25.01.2003)	GB
0324655.0	22 October 2003 (22.10.2003)	GB

(71) Applicant *(for all designated States except US)*: **OXFORD GLYCOSCIENCES (UK) LTD** [GB/GB]; The Forum, 86 Milton Park, Abingdon, Oxfordshire OX14 4RY (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **SCOPES, David, Ian, Carter** [GB/GB]; The Forum, 86 Milton Park, Abingdon, Oxfordshire OX14 4RY (GB).

(74) Agent: **THOMPSON, John**; c/o Celltech R & d Ltd, 208 Bath Road, Slough, Berkshire SL1 3WE (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED PHENYLUREA DERIVATIVES AS HDAC INHIBITORS

(57) Abstract: A series of phenylurea derivatives, further substituted on the phenyl ring by a benzoxazole, benzothiazole or benzimidazole moiety, being inhibitors of histone deacetylase, are accordingly of use in medicine, in particular for the treatment of cancer.

WO 2004/067480 A2

SUBSTITUTED PHENYLUREA DERIVATIVES AS HDAC INHIBITORS

The present invention relates to novel compounds that are useful as inhibitors of histone deacetylase. It also relates to methods for their synthesis, pharmaceutical compositions comprising the novel compounds and their use in medicine, in particular for the treatment of cancer.

DNA in eukaryotic cells is tightly associated with histone proteins to form nucleosomes, which represent the basic structure of chromatin. The histones can be reversibly modified by a number of post-translational reactions, such as phosphorylation, methylation, ADP-ribosylation and acetylation (Davie J R & Spencer V A (1999) J. Cell. Biochem., Suppl 32-33, 141-8).

The dynamic state of histone acetylation is tightly regulated and maintained by two enzyme activities: *histone acetyltransferases* and *histone deacetylases*. Acetylation of histones is a reversible modification that occurs during the assembly of nucleosomes and during DNA synthesis and transcription. Histone hyperacetylation correlates with an open decondensed chromatin structure and gene activation, while hypoacetylation correlates with chromatin condensation and transcriptional repression (Katan-Khaykovich Y & Struhl K (2002) Genes Dev., Mar 15, 16(6), 743-52).

The enzyme, histone deacetylase catalyses the removal of the acetyl group from the free amino group of lysine residues on the N-terminal part of the nucleosome bound histone. Thus at physiological pH, the liberated lysine residues of the histones confer a positive charge, which can associate with the negatively charged phosphate groups of the DNA. This stronger association results in a tighter conformational configuration that prevents transcriptional activators binding to their DNA promoter sites and effectively deactivates gene expression (Davie J R & Spencer V A (1999) J. Cell. Biochem., Suppl 32-33, 141-8). Commonly histone deacetylases will exist associated in a multi-protein complex that includes transcription repressor proteins, e.g. mSin3A, (David et al., (1998) Oncogene, 16, 2549-2556 & Ayer DE, (1999) Trends Cell Biol., May, 9(5), 193-8). Conversely, the opposing enzyme, histone acetylase, is found complexed/associated with transcription activators and indeed some transcriptional activators have intrinsic histone acetylase activity (Strahl BD & Allis CD (2000) Nature, 403, 41).

Several human histone deacetylase (HDAC) enzymes have been identified and classified based on their similarity to known yeast factors. They are grouped into three classes as follows: Class I HDACs are similar to the yeast transcriptional repressor yRPD3, while class II HDACs are related to yeast yHDA1 and class III HDACs to yeast Sir2 homologue ySIR2.

Thus, reversible histone acetylation is a major regulatory mechanism that modulates gene expression. This regulation of transcription essentially controls cellular processes such as cellular differentiation and cellular growth.

Aberrant activity of either histone acetylase or histone deacetylase is a key event in the onset and progression of cancer. Thus inhibition of histone deacetylase activity in malignant cells can result in the reversal of the malignant phenotype via the re-expression of previously 'repressed' or 'silenced' genes. Previous research has shown that histone deacetylase inhibitors can reactive gene expression and inhibit the growth and survival of cancerous cells (Reviewed in Johnstone RW, 2002, Nat. Rev. Drug Discov., Apr;1(4):287-99). For example, it has been demonstrated that histone deacetylase inhibitors can induce differentiation in some myeloid leukemia cell lines (reviewed in Melnick A, Licht JD. (2002) Curr. Opin. Hematol., Jul, 9(4), 322-32).

Histone deacetylases have also been implicated in localised angiogenesis (Kim MS et al., 2001, Nat. Med., Apr;7(4), 437-43) and cell-mediated inflammation processes (Takahashi I et al., 1996, J. Antibiot., (Tokyo) May, 49(5), 453-7). These are processes, which may contribute to skin disorders such

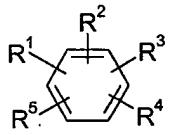
as psoriasis and therefore, histone deacetylase inhibitors may also find use in the treatment of proliferative skin disorders, such as but not limited to, psoriasis.

Several classes of compounds have been identified that inhibit histone deacetylase activity e.g. trichostatin A (TSA), trapoxin, suberoylanilide hydroxamic acid (SAHA), phenylbutyrate and other butyrate derivatives amongst others and these are described and reviewed in Furumai R et al., 2001 Proc. Natl. Acad. Sci., U S A, Jan 2; 98(1): 87-92; Johnstone, Ricky W (2002) Nature Reviews Drug Discovery, 1(4), 287-299; Gore, Steven D. & Carducci, Michael A, Expert Opinion on Investigational Drugs, (2000), 9(12), 2923-2934, Yoshida M et al., (2001) Cancer Chemother. Pharmacol., Aug;48 Suppl 1:S20-6);
WO02/50285 and WO02/26696.

However, there remains a need for novel histone deacetylase inhibitors for use as therapeutic agents in the treatment of cancer and other proliferative disorders, such as psoriasis. In particular the need is for compounds that are potent in vivo and yet exhibit minimal or controllable side-effects.

The present invention provides a class of compounds, which can be used as inhibitors of histone deacetylases. These compounds provide the opportunity for establishing new treatments for cancer, angiogenesis, inflammatory and autoimmune conditions, cardiovascular diseases and proliferative disorders of the skin.

The invention provides a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof:



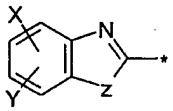
(I)

wherein

R^1, R^2 and R^3 are independently, hydrogen, halogen, CF_3, OR^6, NR^7R^8, NR^8COR^{10}, $NR^8SO_2R^{10}$ or C_{1-6} alkyl optionally substituted by hydroxyl or C_{1-6} alkoxy;

R^4 is $NR^8CONR^8R^9$;

R^5 is



wherein one of X and Y is R^{11} and the other is hydrogen or halogen; or X and Y together with the carbon atoms to which they are attached form a fused six-membered aromatic ring; Z is NR^8, O or S;

R^6 is hydrogen or C_{1-6} alkyl, C_{3-6} alkenyl or C_{3-6} alkynyl any of which can optionally be substituted by hydroxyl, C_{1-6} alkoxy or NR^7R^8;

R^7 is hydrogen or C_{1-6} alkyl or C_{3-6} alkenyl either of which can optionally be substituted by C_{1-6} alkoxy;

R^8 is hydrogen or C_{1-6} alkyl;

or the groups R^7 and R^8 may together with the nitrogen to which they are attached form a 5- or 6-membered ring which optionally contains up to two further heteroatoms selected from NR^8, S and O;

R^9 is C_{1-10} alkyl or C_{3-10} alkenyl wherein a $-CH_2-$ group other than that adjacent to the N may be replaced by -O- and wherein the alkyl or alkenyl is substituted by one or more hydroxamic acid groups (CONHOH);

or in R^4 the groups R^8 and R^9 may together with the nitrogen to which they are attached form a 5- or 6-membered ring, which is substituted with one or more hydroxamic acid groups (CONHOH);

R^{10} is C_{1-6} alkyl; and

R^{11} is hydrogen, halogen, C_{1-6} alkyl, CF_3, OCF_3, CN, OR^6 or phenyl optionally substituted by one or more substituents selected from halogen, C_{1-6} alkyl, CF_3, OCF_3, OR^6, CN and methylenedioxo; or a 5- to 10-membered heteroaryl group containing up to three heteroatoms selected from O, N and S, which heteroaryl group may optionally be substituted by one or more substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy and halogen.

Preferably R^1, R^2 and R^3 are independently, hydrogen, halogen, OR^6, NR^7R^8, or C_{1-6} alkyl optionally substituted by hydroxyl or C_{1-6} alkoxy.

Preferably Z is O.

Preferably R^6 is hydrogen or C_{1-6} alkyl or C_{3-6} alkenyl either of which can optionally be substituted by hydroxyl or C_{1-6} alkoxy.

Preferably R^9 is substituted by one hydroxamic acid group (CONHOH).

More preferably R^1 is hydrogen, OR^6 or NR^7R^8.

More preferably R^2 is hydrogen.

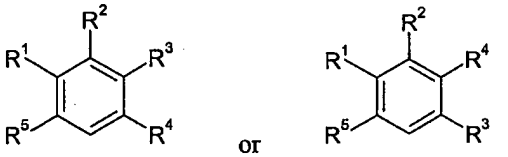
More preferably R^3 is hydrogen, halogen or OR^6.

In the group NR^7R^8, when the R^7 and R^8 substituents, together with the nitrogen to which they are attached form a 5- or 6- membered ring, the ring may be, for example, morpholine, piperazine or N-methyl piperazine.

When R^{11} is a 5- to 10-membered heteroaryl group containing up to three heteroatoms selected from O, N and S, the group may be, for example, benzofuran e.g. 2-benzofuran, benzothiophene e.g. 2-benzothiophene, benzoxazole e.g. 2-benzoxazole, benzothiazole e.g. 2-benzothiazole, quinoline, isoquinoline, pyridine, pyrimidine, pyrazine, oxadiazole, imidazole, tetrazole, furan and thiophene.

A specific group of compounds which may be mentioned are those where R^{11} is hydrogen, halogen, e.g. fluoro, C_{1-6} alkyl, CF_3, OCF_3, CN, OR^6, e.g. methoxy, or phenyl.

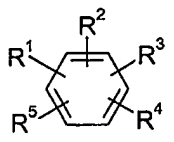
The configuration of the R groups is preferably,



The term "alkyl" as used herein whether on its own or as part of a larger group e.g. "alkoxy" includes both straight and branched chain radicals. The term alkyl also includes those radicals wherein one or more hydrogen atoms are replaced by fluorine, e.g. CF_3.

The term "alkenyl" and "alkynyl" as used herein includes both straight and branched chain radicals.

A group of compounds of the invention which may be mentioned are those of formula (Ia) and pharmaceutically acceptable salts and prodrugs thereof:



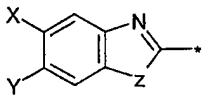
(I)

wherein

R^1, R^2 and R^3 are independently, hydrogen, halogen, CF_3, OR^6, NR^7R^8, NR^8COR^{10}, $NR^8SO_2R^{10}$ or C_{1-6} alkyl optionally substituted by hydroxyl or C_{1-6} alkoxy;

R^4 is $NR^8CONR^8R^9$;

R^5 is



wherein one of X and Y is R^{11} and the other is hydrogen or halogen; or X and Y together with the carbon atoms to which they are attached form a fused six-membered aromatic ring; Z is NR^8, O or S;

R^6 is hydrogen or C_{1-6} alkyl, C_{3-6} alkenyl or C_{3-6} alkynyl any of which can optionally be substituted by hydroxyl, C_{1-6} alkoxy or NR^7R^8;

R^7 is hydrogen or C_{1-6} alkyl or C_{3-6} alkenyl either of which can optionally be substituted by C_{1-6} alkoxy;

R^8 is hydrogen or C_{1-6} alkyl;

or the groups R^7 and R^8 may together with the nitrogen to which they are attached form a 5- or 6-membered ring which optionally contains up to two further heteroatoms selected from NR^8, S and O;

R^9 is C_{1-10} alkyl or C_{3-10} alkenyl wherein a $-CH_2-$ group other than that adjacent to the N may be replaced by -O- and wherein the alkyl or alkenyl is substituted by one or more hydroxamic acid groups (CONHOH);

or in R^4 the groups R^8 and R^9 may together with the nitrogen to which they are attached form a 5- or 6-membered ring, which is substituted with one or more hydroxamic acid groups (CONHOH);

R^{10} is C_{1-6} alkyl; and

R^{11} is hydrogen, halogen, C_{1-6} alkyl, OR^6 or phenyl optionally substituted by one or more substituents selected from halogen, C_{1-6} alkyl, CF_3, OCF_3, OR^6, CN and methylenedioxo; or a 5- to 10-membered heteroaryl group containing up to three heteroatoms selected from O, N and S, which heteroaryl group may optionally be substituted by one or more substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy and halogen.

Preferred specific compounds of the invention include those described in the Examples.

As described herein, for all aspects of the invention, reference to compounds of formula (I) encompasses the pharmaceutically acceptable salts and prodrugs thereof.

Suitable, pharmaceutically acceptable salts of the compounds of formula (I) include, but are not limited to, salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate, or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate, and stearate. Salts may be prepared in a conventional manner using methods well known in the art.

The invention also includes prodrugs of the aforementioned compounds. A prodrug is commonly described as an inactive or protected derivative of an active ingredient or a drug, which is converted to the active ingredient or drug in the body.

In addition, the invention extends to active derivatives of the aforementioned compounds.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

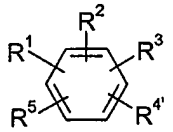
Certain of the compounds of formula (I) may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses. Where a compound contains an alkene moiety, the alkene can be presented as a cis or trans isomer or a mixture thereof. When an isomeric form of a compound of the invention is provided substantially free of other isomers, it will preferably contain less than 5% w/w, more preferably less than 2% w/w and especially less than 1% w/w of the other isomers.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably at least 10% of a compound of the formula (I) or pharmaceutically acceptable derivative thereof.

The compounds of formula (I) can be prepared by art-recognized procedures from known or commercially available starting materials. If the starting materials are unavailable from a commercial source, their synthesis is described herein, or they can be prepared by procedures known in the art.

The invention also provides a process for preparing a compound of formula (I) from a corresponding protected oxyamide intermediate compound, i.e. a compound as defined in formula (I), wherein the one or more hydroxamic acid groups (CONHOH) are replaced by CONHOP wherein P is a protecting group, for example, benzyloxyamide or *tert*-butyldimethylsilyloxyamide, by hydrogenation e.g. with palladium on a charcoal catalyst in dioxane or by cleavage with acid, e.g. hydrochloric acid or trifluoroacetic acid. The acid mediated removal of the *tert*-butyldimethylsilyl group can be performed as a separate step or can be performed as part of the work-up procedure.

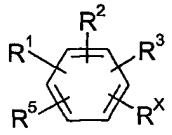
The protected oxyamide intermediate compound may be prepared by conversion of the corresponding free acid of formula (II):



(II)

wherein R^1, R^2, R^3 and R^5 are as defined for formula (I) and $R^{4'}$ is $NR^8CONR^8R^A$ where R^8 is as defined for formula (I) and R^A is C_{1-10} alkyl or C_{3-10} alkenyl wherein a $-CH_2-$ group other than that adjacent to the N may be replaced by -O- and wherein the alkyl or alkenyl is substituted with one or more carboxylic acid groups; by coupling with a protected hydroxylamine, for example, benzylhydroxylamine or *tert*-butyldimethylsilylhydroxylamine in THF under an argon atmosphere. An ester compound of formula (II) can be converted to a free acid compound of formula (II) by hydrolysis, using methods well known to those skilled in the art.

A compound of formula (II) may be prepared from a compound of formula (III):



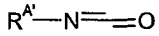
(III)

wherein R^X is NO_2, NHR^8, or NCO and R^1, R^2, R^3, R^5 and R^8 are as defined for formula (I), by the methods described below:

A compound of formula (III) where R^X is NH_2 may be prepared from a corresponding compound where R^X is NO_2 by methods well known to those skilled in the art, for example, hydrogenation with palladium on a charcoal catalyst or treatment with Zn and acetic acid. A compound of formula (III) wherein R^X is NH_2 may be converted to a compound of formula (III) wherein R^X is NCO by reaction with, for example, triphosgene. A compound of formula (III) wherein R^X is NH_2 may be converted to another compound of formula (III) wherein R^X is NHR^8 and R^8 is C_{1-6} alkyl, by an alkylation or reductive amination reaction using methods well known to those skilled in the art.

A process for preparing a compound of formula (II), comprises:

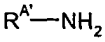
treating a compound of formula (III) wherein R^X is NHR^8, with a compound of formula (IV):



(IV)

wherein $R^{A'}$ is C_{1-10} alkyl or C_{3-10} alkenyl wherein a $-CH_2-$ group other than that adjacent to the N may be replaced by -O- and wherein the alkyl or alkenyl is substituted with one or more carboxylate ester groups, e.g. by stirring at room temperature or with heating in a suitable solvent, for example THF.

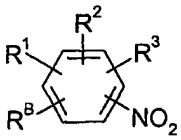
Alternatively, a compound of formula (III) wherein R^X is NCO, is treated with a compound of formula (V):



(V)

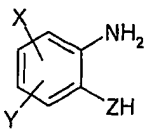
wherein $R^{A'}$ is as defined for formula (IV), e.g. by stirring at room temperature or with heating in a suitable solvent. Compounds of formula (IV) and (V) may be available through the usual commercial sources. They and derivatives thereof may also be prepared by methods well known to those skilled in the art.

The compounds of formula (III) wherein R^X is NO_2, R^1, R^2, R^3 and R^5 are as defined for formula (I) and Z is O or S, may be prepared by treatment of a compound of formula (VI) wherein R^1, R^2 and R^3 are as defined for formula (I) and R^B is CO_2H or CHO:



(VI)

with a compound of formula (VII) wherein X and Y are as defined for formula (I) and Z is S or O:

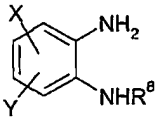


(VII)

by e.g. either (i) heating in a condensation/cyclisation reaction, using for example polyphosphoric acid, or (ii) by firstly coupling a compound of formula (VI) to a compound of formula (VII) via either an ester/ thioester or amide formation reaction using methods well known to those of skill in the art followed by direct heating or heating with an acidic media with a suitable solvent to effect cyclisation, for example, p-toluenesulfonic acid in toluene. Alternatively, this may be achieved via oxidative cyclisation of a Schiff base, derived from the condensation of the 2-aminophenol or 2-aminothiophenol and aldehydes, using various oxidants such as $PhI(OAc)_2$, $Pb(OAc)_4$ or DDQ.

Compounds of formulae (VI) and (VII) may be available through the usual commercial sources. They and derivatives thereof may also be prepared by methods well known to those skilled in the art.

The compounds of formula (III) wherein R^X is NO_2, R^1, R^2, R^3 and R^5 are as defined for formula (I) and Z is NR^8, may be prepared by treatment of a compound of formula (VI) with a compound of formula (VIII):



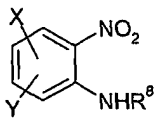
(VIII)

wherein X, Y and R^8 are as defined for formula (I) in e.g. the following reactions:

(i) if R^B in compound (VI) is CO_2H, heating in a condensation/cyclisation reaction using for example polyphosphoric acid; or

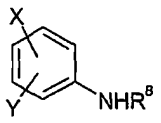
(ii) if R^B in compound (VI) is CHO, heating in acetonitrile followed by oxidation using for example $O_2/FeCl_3$ (cat.) in acetonitrile.

Compounds of formula (VIII) may be prepared by reduction of compounds of formula (IX) wherein X, Y and R^8 are as defined for formula (I) by methods well known to those skilled in the art, for example, hydrogenation with palladium on a charcoal catalyst or treatment with Zn and acetic acid:



(IX)

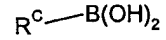
Compounds of formula (IX) may be prepared by nitration of compounds of formula (X) wherein X, Y and R^8 are as defined for formula (I), by methods well known to those skilled in the art, for example using fuming nitric acid and sulfuric acid or fuming nitric acid and tin(IV) chloride:



(X)

Compounds of formula (X) may be available through the usual commercial sources. They and derivatives thereof may also be prepared by methods well known to those skilled in the art.

The compounds of formula (III), wherein X or Y is halogen, can be modified to give a corresponding set of compounds of formula (III) wherein X or Y is phenyl or a 5- to 10-membered heteroaryl group either of which is optionally substituted by one or more substituents as defined in formula (I). The modification may be achieved by a coupling reaction with compounds of formula (XI) using an appropriate catalyst for example tetrakis (triphenylphosphine) palladium:



(XI)

where R^C is phenyl or a 5- to 10-membered heteroaryl group either of which is optionally substituted by one or more substituents as defined for formula (I).

Additionally, compounds of formula (III) where R^X is NO_2, R^3 is halogen at a position ortho or para to the R^X group and R^1, R^2 and R^5 are as defined for formula (I) may be converted to a corresponding subset of compounds of formula (III) where R^3 is OR^6 or NR^7R^8, by reaction with an alcohol or amine via a nucleophilic aromatic substitution.

Compounds of formula (III) where R^3 is NR^8COR^{10} or $NR^8SO_2R^{10}$ may be prepared from corresponding compounds of formula (III) where R^3 is NHR^8 by reaction with the appropriate carboxylic acid/chloride or sulfonyl chloride, i.e. $R^{10}CO_2H/(R^{10}CO_2Cl)$ or $R^{10}SO_2Cl$ wherein R^{10} is as defined for formula (I).

During the synthesis of the compounds of formula (I), labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. The protecting groups may be removed at any stage in the synthesis of the compounds of formula (I) or may be present on the final compound of formula (I). A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in for example *Protective Groups in Organic Chemistry,* T.W. Greene and P.G.M. Wuts (Wiley-Interscience, New York, 2nd edition, 1991).

Further details for the preparation of compounds of formula (I) are found in the examples.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds of formula (I). Libraries of compounds of formula (I) may be prepared by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I) or pharmaceutically acceptable salts and prodrugs thereof.

The pharmaceutically acceptable salts and prodrugs of the compounds of formula (I) may be prepared by methods well known to those skilled in the art.

Any novel intermediate compounds as described herein also fall within the scope of the present invention. In particular the invention provides a compound as defined by formula (I) wherein the one or more hydroxamic acid groups (CONHOH) are replaced by CONHOP wherein P is a protecting group e.g. benzyloxyamide, *tert*-butyldimethylsilyloxyamide or *tert*-butyldiphenylsilyloxyamide.

Preferred intermediate compounds include those described in the examples.

The pharmaceutically effective compounds of formula (I) may be administered in conventional dosage forms prepared by combining a compound of formula (I) ("active ingredient") with standard pharmaceutical carriers or excipients according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof, together with one or more pharmaceutically acceptable carriers or excipients.

The active ingredient or pharmaceutical composition can be administered simultaneously, separately or sequentially with another appropriate treatment for cancer, angiogenesis, inflammatory and autoimmune conditions, cardiovascular diseases and proliferative disorders of the skin.

The active ingredient or pharmaceutical composition may be administered to a subject by any of the routes conventionally used for drug administration, for example they may be adapted for oral (including buccal, sublingual), topical (including transdermal), nasal (including inhalation), rectal, vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) administration to mammals including humans. The most suitable route for administration in any given case will depend on the particular compound or pharmaceutical composition, the subject, and the nature and severity of the disease and the physical condition of the subject. Such compositions may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical compositions adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulfate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Pharmaceutical compositions adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, impregnated dressings, sprays, aerosols or oils and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. Such applications include those to the eye or other external tissues, for example the mouth and skin and the compositions are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base. The composition may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions.

Pharmaceutical compositions adapted for topical administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical compositions adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical compositions adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical compositions adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable compositions wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical compositions adapted for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical compositions adapted for rectal administration may be presented as suppositories or enemas. Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

Pharmaceutical compositions adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray compositions.

Pharmaceutical compositions adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

For parenteral administration, fluid unit dosage forms are prepared utilizing the active ingredient and a sterile vehicle, water being preferred. The active ingredient, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the active ingredient can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the active ingredient is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The active ingredient can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active ingredient.

The pharmaceutical compositions according to the invention are preferably adapted for oral administration.

It should be understood that in addition to the ingredients particularly mentioned above, the compositions may also include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents. They may also contain therapeutically active agents in addition to the compounds of the present invention. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration.

Pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per dose. Such a unit may contain for example 0.1mg/kg to 750mg/kg, more preferably 0.1mg/kg to 10mg/kg depending on the condition being treated, the route of administration and the age, weight and condition of the patient. Preferred unit dosage compositions are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of compounds in the first and second aspects of the invention will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular subject being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the aforementioned compounds given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

No toxicological effects are indicated when the aforementioned compounds of formula (I) are administered in the above mentioned dosage range.

The compounds of the present invention are useful in that they are capable of inhibiting histone deacetylase activity. Thus, the compounds can be used in the treatment of cancer.

The compounds of the present invention can also be used in combination with one or more additional treatments or therapeutic compounds for cancer. Examples of such treatments include, surgery and radiation therapy. Examples of therapeutic compounds include but are not limited to cisplatin, cyclophosphamide, methotrexate, 5-fluorouracil, paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, doxorubicin, tamoxifen, toremifene, megestrol acetate, anastrozole, goserelin, anti-HER2 monoclonal antibody, capecitabine and raloxifene hydrochloride.

The compounds of the present invention can also be used in the treatment of angiogenesis and angiogenesis dependent diseases, which include angiogenesis associated with the growth of solid tumours and retinopathy.

The compounds of the present invention can also be used in combination with one or more additional treatments or therapeutic compounds for angiogenesis. Examples of such other therapeutic compounds include, but are not limited to, recombinant platelet-derived growth factor-BB (Regranex™).

The compounds of the present invention can also be used in the treatment of inflammatory conditions, including, but not limited to, rheumatoid arthritis, inflammatory bowel disease, and wound healing.

The compounds of the present invention can also be used in the treatment of proliferative skin disorders, such as, but not limited to psoriasis.

By the term "treating" is meant either prophylactic or therapeutic therapy.

The term cancer or 'carcinoma' is a malignant new growth that arises from epithelium, found in skin or, more commonly, the lining of body organs. Carcinomas tend to infiltrate into adjacent tissues and spread (metastasise) to distant organs, for example to bone, liver lung or the brain. Herein, cancer includes both metastatic tumour cells and tissue and examples include, but are not limited to, melanoma, mesothelioma, lymphoma, leukaemia, fibrosarcoma, rhabdomyosarcoma, mastocytoma and the following tissue -carcinomas: colorectal, colon, prostate, lung, breast, pancreatic, intestinal, renal, gastric, bladder, ovarian, uterine, cervical, hepatic and stomach.

In additional aspects, therefore, the present invention provides:

(i) the use of a compound of formula (I) in the manufacture of a medicament for the inhibition of histone deacetylase enzyme activity.

(ii) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of cancer.

(iii) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of angiogenesis and angiogenesis dependent diseases which include angiogenesis associated with the growth of solid tumours and retinopathy.

(iv) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of inflammatory conditions such as but not limited to rheumatoid arthritis, inflammatory bowel disease, and wound healing.

(v) a method for the treatment of cancer, which comprises the step of administering to a patient an effective amount of a compound of formula (I).

(vi) a method for the treatment of angiogenesis and angiogenesis dependent diseases, which include angiogenesis associated with the growth of solid tumours and retinopathy, which comprises the step of administering to a patient an effective amount of a compound of formula (I).

(vii) a method for the treatment of inflammatory diseases, such as but not limited to rheumatoid arthritis, inflammatory bowel disease, and wound healing which comprises the step of administering to a patient an effective amount of a compound of formula (I).

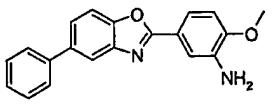
All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The invention will now be described by reference to the following examples, which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

Example 1:

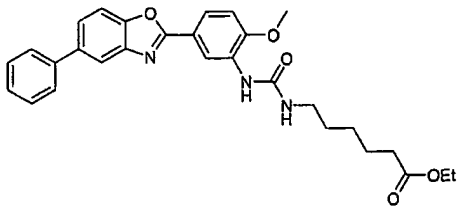
6-[3-[2-Methoxy-5-(5-phenylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide

(a) 2-(3-Amino-4-methoxyphenyl)-5-phenylbenzoxazole



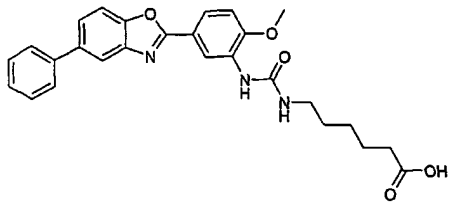
3-Amino-4-methoxybenzoic acid (3.0mmol) and 2-amino-4-phenylphenol (3.0mmol) were mixed in polyphosphoric acid (5ml) and the mixture was heated to 200°C for 4 h. The reaction mixture was slowly poured into ice water (100ml) and the resulting mixture basified with solid sodium hydroxide. At pH5-6 the precipitate was filtered, washed with water and dried under vacuum. MS (APCI-) *m/z* 317.

(b) 6-[3-[2-Methoxy-5-(5-phenylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid ethyl ester



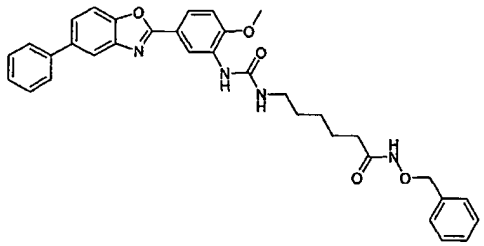
Ethyl 6-isocyanatohexanoate (36μL, 0.2mmol) was added to a solution of 2-(3-amino-4-methoxy-phenyl)-5-phenylbenzoxazole (0.2mmol) in THF (2ml). After stirring overnight at 40°C the reaction was concentrated under reduced pressure to give the product. MS (APCI-) *m/z* 500.1

(c) 6-[3-[2-Methoxy-5-(5-phenylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid



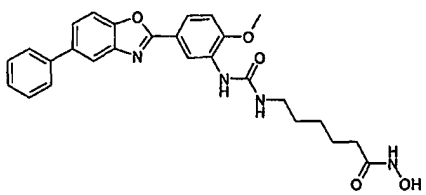
6-[3-[2-Methoxy-5-(5-phenylbenzoxazole-2-yl)phenyl]ureido]hexanoic ethyl ester (0.2mmol) in THF/MeOH (1:1, 1.5ml) was added to a solution of LiOH (24mg 1.0 mmol) in water (0.5ml). After stirring for 6h the reaction was acidified with 2M HCl and the resulting precipitate filtered and dried under vacuum. ^{1}H NMR (DMSO): δ 1.21-1.50 (6H, m), 2.23 (2H, t), 3.11 (2H, q), 3.96 (3H, s), 6.98 (1H, t), 7.19 (1H, d), 7.39 (1H, m), 7.49 (2H, t), 7.75 (5H, m), 8.00 (1H, d), 8.13 (1H, s), 9.08 (1H, d). MS (APCI-) *m/z* 472.0.

(d) 6-[3-[2-Methoxy-5-(5-phenylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid benzyloxyamide



To a stirred solution of 6-[3-[2-methoxy-5-(5-phenylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid (200mg, 0.42mmol) in THF (10ml) under an argon atmosphere was added 2-chloro-4,6-dimethoxy-1,3,5-triazine (89mg, 0.51mmol) followed by 4-methylmorpholine (128mg, 1.27mmol). After stirring for 1h, benzylhydroxylamine hydrochloride (67.4mg, 0.42mmol) was added. After stirring overnight the reaction was quenched with water (10ml) and extracted with ethyl acetate (2x50ml). The organic fractions were combined and washed with saturated sodium hydrogen carbonate solution (50ml), 2M hydrochloric acid solution (50ml), saturated sodium chloride solution (50ml), dried (Na_2SO_4) and concentrated. This crude product was then subjected to flash silica gel column chromatography using ethyl acetate as eluant to give the subtitle compound, 47mg (19%). ^{1}H NMR (DMSO) δ 1.25 (2H, m), 1.48 (4H, m), 1.97 (2H, t), 3.11 (2H, m), 3.94 (3H, s), 4.76 (2H, s), 6.98 (1H, m), 7.19 (1H, d), 7.36 (6H, m), 7.50 (2H, t), 7.65-7.87 (5H, m), 8.01 (1H, d), 8.16 (1H, s), 9.09 (1H, s), 10.97 (1H, s). MS (APCI-) *m/z* 577.

(e) 6-[3-[2-Methoxy-5-(5-phenylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide



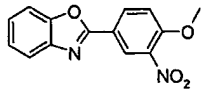
To a stirred solution of 6-[3-[2-methoxy-5-(5-phenylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid benzyloxyamide (41mg, 0.07mmol) in dioxane (10ml) under an argon atmosphere was added 10% Pd on charcoal (80mg). The flask was then evacuated and flushed with hydrogen. After stirring for 2 days the reaction mixture was filtered through a pad of celite, washed with further dioxane (50ml) and concentrated to give the title compound 25mg (75%). ^{1}H NMR (DMSO) δ 1.30 (2H, m), 1.50 (4H, m),

1.98 (2H, m), 3.10 (2H, m), 3.95 (3H, s), 7.00 (1H, m), 7.20 (1H, d), 7.38 (1H, m), 7.50 (2H, t), 7.65-7.88 (5H, m), 8.03 (1H, d), 8.15 (1H, s), 8.59 (1H, s), 9.05 (1H, s), 10.36 (1H, s). MS (APCI-) *m/z* 487.

Example 2:

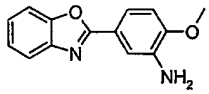
6-[3-[2-Methoxy-5-(benzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide

(a) 2-(4-Methoxy-3-nitrophenyl)benzoxazole



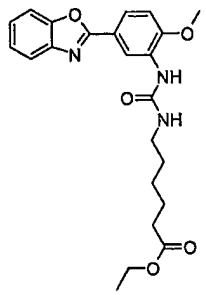
To a stirred solution of 2-aminophenol (2.77g, 25.4mmol) in tetrahydrofuran (100ml) was added dropwise a solution of 4-methoxy-3-nitrobenzoyl chloride (5.47g, 25.4mmol). After stirring overnight the solvent was removed under reduced pressure. The solid was suspended in toluene (150ml) and *p*-toluenesulfonic acid (10.13g, 53.3mmol) was added. This was heated to reflux for 4h under Dean Stark conditions. The solution was allowed to cool and partitioned between ethyl acetate (100ml) and saturated sodium hydrogen carbonate solution (200ml). The aqueous phase was extracted with ethyl acetate (2×50ml) and the combined organic extracts were washed with 2M hydrochloric acid (2×50ml), water (50ml), saturated sodium chloride solution (50ml), dried (Na_2SO_4) and concentrated to give the subtitle compound (6.83g, 99%). ^{1}H NMR (DMSO): δ 4.05 (3H, s), 7.43-7.45 (2H, m), 7.62 (1H, d), 7.79-7.83 (2H, m), 8.45 (1H, dd), 8.63 (1H, d).

(b) 2-(3-Amino-4-methoxyphenyl)benzoxazole



To a suspension of 2-(4-methoxy-3-nitrophenyl)benzoxazole (3g, 11.1mmol) in ethyl acetate (200ml) under an argon atmosphere was added 10% Pd on carbon (0.75g). The flask was flushed with hydrogen and the reaction was stirred overnight. The mixture was filtered through a pad of Celite and the solvent was removed under reduced pressure. The crude compound was subjected to flash silica gel column chromatography using light petroleum-ethyl acetate (2:1/1:1) as eluant to give the subtitle compound (2.11g, 79%). ^{1}H NMR (DMSO): δ 3.87 (3H, s), 5.13 (2H, s), 6.99 (1H, d), 7.34-7.39 (2H, m), 7.43 (1H, dd), 7.51 (1H, d), 7.70-7.75 (2H, m).

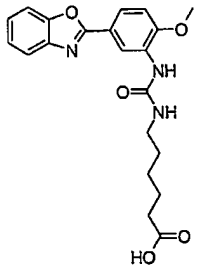
(c) 6-[3-[5-(Benzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid ethyl ester



To a stirred solution of 2-(3-amino-4-methoxyphenyl)benzoxazole (1.00g, 4.16mmol) in tetrahydrofuran (30ml) was added ethyl 6-isocyanatohexanoate (1.12ml, 6.24mmol) dropwise. The reaction was refluxed at 80°C for 48h. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure. The residue was triturated in ethyl acetate and the solid collected by

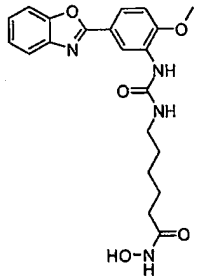
filtration and dried under vacuum to give the subtitle compound (1.36g, 77%). ^{1}H NMR (DMSO): δ 1.17 (3H, t), 1.28-1.36 (2H, m), 1.40-1.47 (2H, m), 1.51-1.61 (2H, m), 2.30 (2H, t), 3.10 (2H, q), 3.95 (3H, s), 4.04 (2H, q), 6.98 (1H, t), 7.19 (1H, d), 7.35-7.41 (2H, m), 7.73-7.80 (3H, m), 8.13 (1H, s), 9.06 (1H, d).

(d) 6-[3-[5-(Benzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid



A solution of lithium hydroxide (0.319g, 13.33mmol) in water (7ml) was added to a solution of 6-[3-[5-(benzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid ethyl ester (1.13g, 2.67mmol) in tetrahydrofuran (21ml) and the reaction was stirred vigorously at 50°C overnight. The resulting suspension was acidified with 2M hydrochloric acid and the precipitate was collected by filtration to give the subtitle compound (0.95g, 90%). ^{1}H NMR (DMSO): δ 1.28-1.36 (2H, m), 1.40-1.58 (4H, m), 2.23 (2H, t), 3.11 (2H, q), 3.95 (3H, s), 6.98 (1H, t), 7.19 (1H, d), 7.35-7.40 (2H, m), 7.74-7.78 (3H, m), 8.13 (1H, s), 9.06 (1H, d), 12.04 (1H, bs).

(e) 6-[3-[5-(Benzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid hydroxyamide

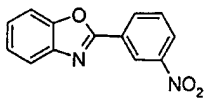


To a stirred suspension of 6-[3-[5-(benzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid (500mg, 1.26mmol) in tetrahydofuran (50ml) under an argon atmosphere was added 2-chloro-4,6-dimethoxy-1,3,5-triazine (376mg, 2.14mmol) followed by N-methylmorpholine (0.41ml, 3.77mmol). After stirring for 1 h *tert*-butyldimethylsilyl hydroxylamine (278mg, 1.89mmol) was added. After stirring over 48 hours the reaction mixture was quenched with water (50ml) and extracted with ethyl acetate (3×50ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (2×50ml) followed by 2M hydrochloric acid (2×50ml). The product, which precipitated during the 2M hydrochloric acid treatment, was collected by filtration, washed with water and freeze dried to give the title compound, (0.159g, 30%). ^{1}H NMR (DMSO): δ 1.22 (2H, m), 1.39-1.57 (4H, m), 1.96 (2H, t), 3.10 (2H, q), 3.95 (3H, s), 6.98 (1H, t), 7.19 (1H, d), 7.35-7.42 (2H, m), 7.73-7.80 (3H, m), 8.13 (1H, s), 8.69 (1H, d), 9.06 (1H, d), 10.36 (1H, bs). MS (APCI+) *m/z* 413.2, (APCI-) *m/z* 411.0.

Example 3:

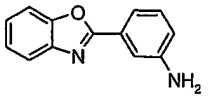
6-[3-[3-(Benzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide

(a) 2-(3-Nitrophenyl)benzoxazole



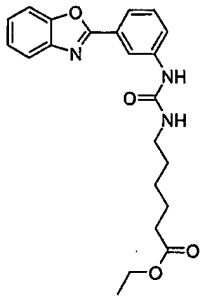
Prepared by the method of Example 2a) from 2-aminophenol (1.63g, 15.0mmol) and 3-nitrobenzoyl chloride (2.78g, 15.0mmol) the subtitle compound was obtained, (2.82g, 78%). ^{1}H NMR (DMSO): δ 7.44-7.53 (2H, m), 7.86-7.96 (3H, m), 8.47 (1H, m), 8.61 (1H, d), 8.87 (1H, s).

(b) 2-(3-Aminophenyl)benzoxazole



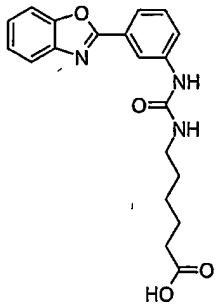
Prepared by the method of Example 2b) from 2-(3-nitrophenyl)benzoxazole (2.82g, 11.7mmol) the subtitle compound was obtained, (2.40g, 97%). ^{1}H NMR (DMSO): δ 5.50 (2H, s), 6.78-6.81 (1H, m), 7.23 (1H, t), 7.33-7.44 (4H, m), 7.77 (2H, m).

(c) 6-[3-[3-(Benzoxazole-2-yl)phenyl]ureido]hexanoic acid ethyl ester



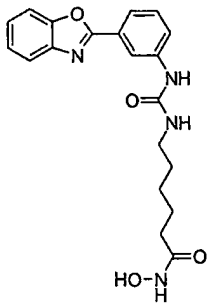
Prepared by the method of Example 2c) from 2-(3-aminophenyl)benzoxazole (1.00g, 4.76mmol) and ethyl 6-isocyanatohexanoate (1.28ml, 7.13mmol) the subtitle compound was obtained, (1.41g, 75%). ^{1}H NMR (DMSO): δ 1.17 (3H, t), 1.25-1.35 (2H, m), 1.41-1.48 (2H, m), 1.50-1.60 (2H, m), 2.30 (2H, t), 3.10 (2H, q), 4.05 (2H, m), 6.24 (1H, t), 7.41-7.47 (4H, m), 7.72-7.82 (3H, m), 8.49 (1H, d), 8.77 (1H, s).

(d) 6-[3-[3-(Benzoxazole-2-yl)phenyl]ureido]hexanoic acid



Prepared by the method of Example 2d) from 6-[3-[3-(benzoxazole-2-yl)phenyl]ureido]hexanoic acid ethyl ester (1.41g, 3.57mmol) and lithium hydroxide (0.43g, 17.84mmol) the subtitle compound was obtained, (1.08g, 82%). ^{1}H NMR (DMSO): δ 1.27-1.35 (2H, m), 1.41-1.58 (4H, m), 2.22 (2H, t), 3.10 (2H, q), 6.24 (1H, t), 7.41-7.47 (4H, m), 7.73 (1H, d), 7.79-7.82 (2H, m), 8.49 (1H, s), 8.77 (1H, s), 12.02 (1H, bs).

(e) 6-[3-[3-(Benzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide

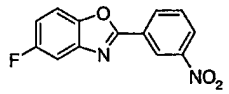


Prepared by the method of Example 2e) from 6-[3-[3-(benzoxazole-2-yl)phenyl]ureido]hexanoic acid (500mg, 1.36mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (406mg, 2.31mmol), N-methylmorpholine (0.45ml, 4.08mmol) and *tert*-butyldimethylsilyl hydroxylamine (301mg, 2.04mmol). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (2×50ml) and then stirred vigorously with 2M hydrochloric acid for 4.5h. The resultant precipitate was collected by filtration, washed with water and freeze dried to give the title compound (191mg, 37%). ^{1}H NMR (DMSO): δ 1.22-1.32 (2H, m), 1.40-1.57 (4H, m), 1.96 (2H, t), 3.10 (2H, q), 6.24 (1H, t), 7.38-7.50 (4H, m), 7.72-7.74 (1H, m), 7.78-7.84 (2H, m), 8.49 (1H, s), 8.69 (1H, s), 8.77 (1H, s), 10.36 (1H, bs). MS (APCI+) *m/z* 383.2, (APCI-) *m/z* 381.0.

Example 4:

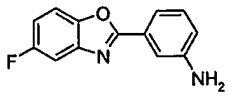
6-[3-[3-(5-Fluorobenzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide

(a) 2-(3-Nitrophenyl)-5-fluorobenzoxazole



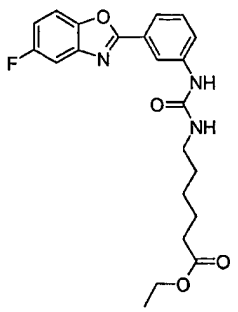
Prepared by the method of Example 2a) from 2-amino-4-fluorophenol (309mg, 2.43mmol) and 3-nitrobenzoyl chloride (500mg, 2.69mmol) the subtitle compound was obtained, (490mg, 78%). ^{1}H NMR (DMSO): δ 7.38 (1H, dt), 7.79 (1H, dd), 7.89-7.96 (2H, m), 8.48 (1H, dd), 8.60 (1H, d), 8.85 (1H, t).

(b) 2-(3-Aminophenyl)-5-fluorobenzoxazole



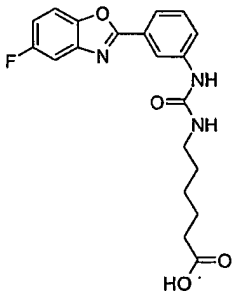
Prepared by the method of Example 2b) from 2-(3-nitrophenyl)-5-fluorobenzoxazole (490mg, 1.90mmol) the subtitle compound was obtained, (419mg, 97%). ^{1}H NMR (DMSO): δ 5.52 (2H, bs), 6.80 (1H, m), 7.21-7.34 (3H, m), 7.42 (1H, s), 7.66 (1H, dd), 7.80 (1H, dd).

(c) 6-[3-[3-(5-Fluorobenzoxazole-2-yl)phenyl]ureido]hexanoic acid ethyl ester



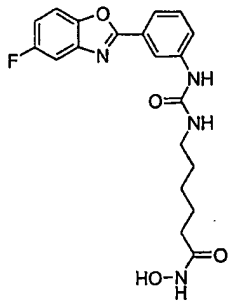
Prepared by the method of Example 2c) from 2-(3-aminophenyl)-5-fluorobenzoxazole (419mg, 1.84mmol) and ethyl 6-isocyanatohexanoate (0.49ml, 2.73mmol) the subtitle compound was obtained, (484mg, 64%). ^{1}H NMR (DMSO): δ 1.17 (3H, t), 1.25-1.35 (2H, m), 1.41-1.60 (4H, m), 2.30 (2H, t), 3.10 (2H, q), 4.05 (2H, q), 6.24 (1H, t), 7.30 (1H, dt), 7.42-7.50 (2H, m), 7.67-7.73 (2H, m), 7.85 (1H, dd), 8.49 (1H, s), 8.78 (1H, s).

(d) 6-[3-[3-(5-Fluorobenzoxazole-2-yl)phenyl]ureido]hexanoic acid



Prepared by the method of Example 2d) from 6-[3-[3-(5-fluorobenzoxazole-2-yl)phenyl]ureido]hexanoic acid ethyl ester (484mg, 1.17mmol) and lithium hydroxide (140mg, 5.85mmol) the subtitle compound was obtained, (445mg, 99%). ^{1}H NMR (DMSO): δ 1.26-1.35 (2H, m), 1.41-1.58 (4H, m), 2.22 (2H, t), 3.10 (2H, q), 6.32 (1H, t), 7.30 (1H, dt), 7.42-7.51 (2H, m), 7.68-7.73 (2H, m), 7.85 (1H, dd), 8.48 (1H, s), 8.89 (1H, s), 12.01 (1H, bs).

e) 6-[3-[3-(5-Fluorobenzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide



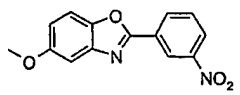
Prepared by the method of Example 2e) from 6-[3-[3-(5-fluorobenzoxazole-2-yl)phenyl]ureido]-hexanoic acid (291mg, 0.76mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (225mg, 1.28mmol), N-methyl morpholine (0.25ml, 2.27mmol) and *tert*-butyldimethylsilyl hydroxylamine (167mg, 1.13mmol). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (2×50ml) and then stirred vigorously with 2M hydrochloric acid for 2.5h. The resultant precipitate was collected by filtration, washed with water and freeze dried to give the title compound (55mg, 18%). ^{1}H NMR

(DMSO): δ 1.22-1.32 (2H, m), 1.40-1.57 (4H, m), 1.96 (2H, t), 3.09 (2H, q), 6.24 (1H, t), 7.31 (1H, dt), 7.42-7.50 (2H, m), 7.68-7.73 (2H, m), 7.85 (1H, dd), 8.49 (1H, s), 8.69 (1H, d), 8.79 (1H, s), 10.36 (1H, s). MS (APCI-) *m/z* 399.0.

Example 5:

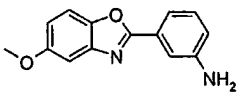
6-[3-[3-(5-Methoxybenzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide

(a) 2-(3-Nitrophenyl)-5-methoxybenzoxazole



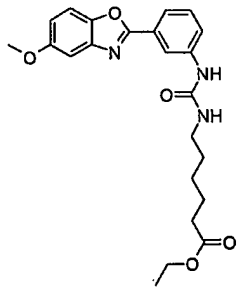
Prepared by the method of Example 2a) from 2-amino-4-methoxyphenol (338mg, 2.43mmol) and 3-nitrobenzoyl chloride (500mg, 2.69mmol) the subtitle compound was obtained, (251mg, 69%). ^{1}H NMR (DMSO): δ 3.84 (3H, s), 7.07 (1H, dd), 7.41 (1H, d), 7.75 (1H, d), 7.91 (1H, t), 8.45 (1H, m), 8.56 (1H, m), 8.82 (1H, t).

(b) 2-(3-Aminophenyl)-5-methoxybenzoxazole



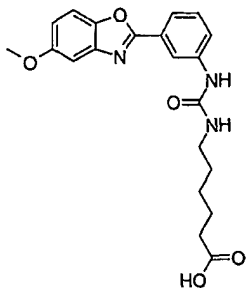
Prepared by the method of Example 2b) from 2-(3-nitrophenyl)-5-methoxybenzoxazole (452mg, 1.67mmol) the subtitle compound was obtained, (369mg, 92%). ^{1}H NMR (DMSO): δ 3.82 (3H, s), 5.49 (2H, bs), 6.79 (1H, m), 6.98 (1H, dd), 7.22 (1H, t), 7.29-7.33 (2H, m), 7.40 (1H, s), 7.65 (1H, d).

(c) 6-[3-[3-(5-Methoxybenzoxazole-2-yl)phenyl]ureido]hexanoic acid ethyl ester



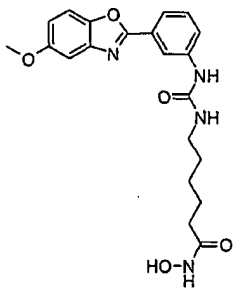
Prepared by the method of Example 2c) from 2-(3-aminophenyl)-5-methoxybenzoxazole (369mg, 1.54mmol) and ethyl 6-isocyanatohexanoate (0.41ml, 2.28mmol) the subtitle compound was obtained, (359mg, 55%). ^{1}H NMR (DMSO): δ 1.17 (3H, t), 1.25-1.35 (2H, m), 1.41-1.60 (4H, m), 2.30 (2H, t), 3.10 (2H, q), 3.83 (3H, s), 4.05 (2H, q), 6.23 (1H, t), 6.01 (1H, dd), 7.36 (1H, d), 7.40-4.49 (2H, m), 7.68-7.70 (2H, m), 8.44 (1H, s), 8.76 (1H, s).

(d) 6-[3-[3-(5-Methoxybenzoxazole-2-yl)phenyl]ureido]hexanoic acid



Prepared by the method of Example 2d) from 6-[3-[3-(5-methoxybenzoxazole-2-yl)phenyl]ureido]hexanoic acid ethyl ester (359mg, 0.84mmol) and lithium hydroxide (101mg, 4.22mmol) the subtitle compound was obtained, (307mg, 92%). ^{1}H NMR (DMSO): δ 1.26-1.35 (2H, m), 1.41-1.58 (4H, m), 2.22 (2H, t), 3.10 (2H, q), 3.83 (3H, s), 6.25 (1H, t), 7.01 (1H, dd), 7.36 (1H, d), 7.41-7.50 (2H, m), 7.70 (2H, d), 8.44 (1H, s), 8.79 (1H, s).

(e) 6-[3-[3-(5-Methoxybenzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide

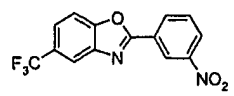


Prepared by the method of Example 2e) from 6-[3-[3-(5-methoxybenzoxazole-2-yl)phenyl]ureido]hexanoic acid (300.1mg, 0.76mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (225.3mg, 1.28mmol), N-methylmorpholine (0.25ml, 2.27mmol) and *tert*-butyldimethylsilyl hydroxylamine. The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (2×50ml) and then stirred vigorously with 2M hydrochloric acid for 20min. The resultant precipitate was collected by filtration, washed with water and freeze dried to give the title compound (174mg, 55%). ^{1}H NMR (DMSO): δ 1.22-1.32 (2H, m), 1.40-1.57 (4H, m), 1.96 (2H, t), 3.09 (2H, q), 3.83 (3H, s), 6.23 (1H, t), 7.01 (1H, dd), 7.36 (1H, d), 7.41-7.49 (2H, m), 7.70 (2H, d), 8.44 (1H, s), 8.69 (1H, d), 8.76 (1H, s), 10.36 (1H, s). MS (APCI-) *m/z* 411.0.

Example 6:

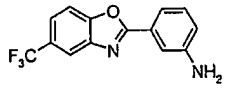
6-[3-[3-(5-Trifluoromethylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide

(a) 2-(3-Nitrophenyl)-5-trifluoromethylbenzoxazole



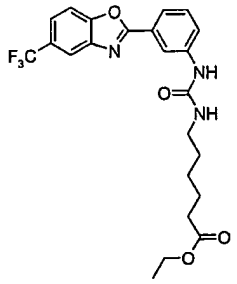
Prepared by the method of Example 2a) from 2-amino-4-(trifluoromethyl)phenol (429.9mg, 2.43mmol) and 3-nitrobenzoyl chloride (500mg, 2.69mmol) the subtitle compound was obtained, (602mg, 80%). ^{1}H NMR (DMSO): δ 7.87 (1H, dd), 7.95 (1H, t), 8.11 (1H, d), 8.32 (1H, s), 8.49-8.53 (1H, m), 8.63 (1H, d), 8.88 (1H, t).

(b) 2-(3-Aminophenyl)-5-trifluoromethylbenzoxazole



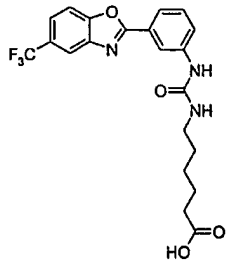
Prepared by the method of Example 2b) from 2-(3-nitrophenyl)-5-trifluoromethylbenzoxazole (602mg, 1.95mmol) the subtitle compound was obtained, (521mg, 96%). ^{1}H NMR (DMSO): δ 5.56 (2H, bs), 6.83 (1H, m), 7.26 (1H, t), 7.37 (1H, d), 7.46 (1H, s), 7.78 (1H, d), 8.01 (1H, d), 8.20 (1H, d).

c) 6-[3-[3-(5-Trifluoromethylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid ethyl ester



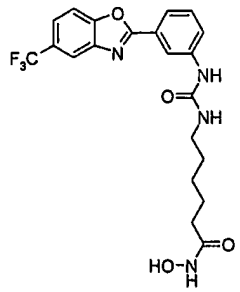
Prepared by the method of Example 2c) from 2-(3-aminophenyl)-5-trifluoromethylbenzoxazole (521mg, 1.87mmol) and ethyl 6-isocyanatohexanoate (0.50ml, 2.79mmol) the subtitle compound was obtained, (704mg, 81%). ^{1}H NMR (DMSO): δ 1.17 (3H, t), 1.27-1.35 (2H, m), 1.41-1.60 (4H, m), 2.30 (2H, t), 3.10 (2H, q), 4.05 (2H, q), 6.25 (1H, t), 7.44-7.52 (2H, m), 7.74-7.82 (2H, m), 8.03-8.05 (1H, d), 8.24 (1H, s), 8.54 (1H, s), 8.81 (1H, s).

(d) 6-[3-[3-(5-Trifluoromethylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid



Prepared by the method of Example 2d) from 6-[3-[3-(5-trifluoromethylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid ethyl ester (704mg, 1.52mmol) and lithium hydroxide (182mg, 7.59mmol) the subtitle compound was obtained, (621mg, 94%). ^{1}H NMR (DMSO): δ 1.26-1.35 (2H, m), 1.41-1.58 (4H, m), 2.22 (2H, t), 3.11 (2H, q), 6.26 (1H, t), 7.45-7.53 (2H, m), 7.75-7.82 (2H, m), 8.05 (1H, d), 8.24 (1H, s), 8.54 (1H, s), 8.81 (1H, s), 12.01 (1H, bs).

(e) 6-[3-[3-(5-Trifluoromethylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide

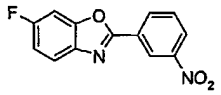


Prepared by the method of Example 2e) from 6-[3-[3-(5-trifluoromethylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid (329mg, 0.76mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (225.3mg, 1.28mmol), N-methylmorpholine (0.25ml, 2.27mmol) and *tert*-butyldimethylsilyl hydroxylamine. The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (2×50ml) and then stirred vigorously with 2M hydrochloric acid for 2h. The resultant precipitate was collected by filtration, washed with water and freeze dried to give the title compound (56mg, 16%). ^{1}H NMR (DMSO): δ 1.22-1.32 (2H, m), 1.40-1.57 (4H, m), 1.96 (2H, t), 3.10 (2H, q), 6.25 (1H, t), 7.44-7.53 (2H, m), 7.74-7.82 (2H, m), 8.05 (1H, d), 8.24 (1H, s), 8.54 (1H, s), 8.69 (1H, s), 8.81 (1H, s), 10.36 (1H, s). MS (APCI-) *m/z* 448.9.

Example 7:

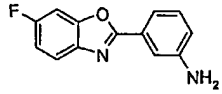
6-[3-[3-(6-Fluorobenzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide

(a) 2-(3-Nitrophenyl)-6-fluorobenzoxazole



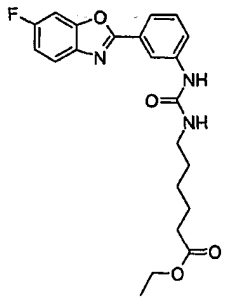
Prepared by the method of Example 2a) from 2-amino-5-fluorophenol (309mg, 2.43mmol) and 3-nitrobenzoyl chloride (500mg, 2.69mmol) the subtitle compound was obtained, (573mg, 91%). ^{1}H NMR (DMSO): δ 7.35 (1H, dt), 7.86-7.95 (3H, m), 8.47 (1H, m), 8.57 (1H, d), 8.83 (1H, m).

(b) 2-(3-Aminophenyl)-6-fluorobenzoxazole



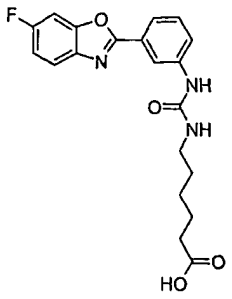
Prepared by the method of Example 2b) from 2-(3-nitrophenyl)-6-fluorobenzoxazole (572mg, 2.22mmol) the subtitle compound was obtained, (483mg, 96%). ^{1}H NMR (DMSO): δ 5.51 (2H, bs), 6.79 (1H, m), 7.20-7.32 (3H, m), 7.40 (1H, t), 7.75-7.82 (2H, m).

(c) 6-[3-[3-(6-Fluorobenzoxazole-2-yl)phenyl]ureido]hexanoic acid ethyl ester



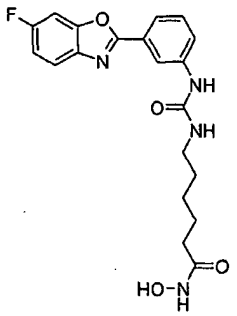
Prepared by the method of Example 2c) from 2-(3-aminophenyl)-6-fluorobenzoxazole (483mg, 2.12mmol) and ethyl 6-isocyanatohexanoate (0.57ml, 3.18mmol) the subtitle compound was obtained, (660mg, 75%). ^{1}H NMR (DMSO): δ 1.17 (3H, t), 1.27-1.35 (2H, m), 1.41-1.60 (4H, m), 2.30 (2H, t), 3.10 (2H, q), 4.05 (2H, q), 6.24 (1H, t), 7.26-7.33 (1H, m), 7.41-7.49 (2H, m), 7.68-7.71 (1H, m), 7.80-7.85 (2H, m), 8.47 (1H, s), 8.78 (1H, s).

(d) 6-[3-[3-(6-Fluorobenzoxazole-2-yl)phenyl]ureido]hexanoic acid



Prepared by the method of Example 2d) from 6-[3-[3-(6-fluorobenzoxazole-2-yl)phenyl]ureido]hexanoic acid ethyl ester (660mg, 1.60mmol) and lithium hydroxide (191mg, 7.97mmol) the subtitle compound was obtained, (611mg, 99%). ^{1}H NMR (DMSO): δ 1.26-1.35 (2H, m), 1.41-1.58 (4H, m), 2.22 (2H, t), 3.10 (2H, q), 6.32 (1H, t), 7.26-7.33 (1H, m), 7.41-7.50 (2H, m), 7.70 (1H, d), 7.81-7.85 (2H, m), 8.47 (1H, s), 8.88 (1H, s), 12.03 (1H, bs).

e) 6-[3-[3-(6-Fluorobenzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide

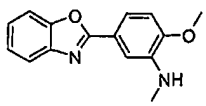


Prepared by the method of Example 2e) from 6-[3-[3-(6-fluorobenzoxazole-2-yl)phenyl]ureido]hexanoic acid (291mg, 0.76mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (225.3mg, 1.28mmol), N-methyl morpholine (0.25ml, 2.27mmol) and *tert*-butyldimethylsilyl hydroxylamine. The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (2×50ml) and then stirred vigorously with 2M hydrochloric acid for 2.5h. The resultant precipitate was collected by filtration, washed with water and freeze dried to give the title compound (79mg, 26%). ^{1}H NMR (DMSO): δ 1.22-1.31 (2H, m), 1.40-1.57 (4H, m), 1.96 (2H, t), 3.09 (2H, q), 6.24 (1H, t), 7.26-7.33 (1H, m), 7.42-7.49 (2H, m), 7.70 (1H, dt), 7.81-7.85 (2H, m), 8.47 (1H, s), 8.69 (1H, s), 8.78 (1H, s), 10.36 (1H, s). MS (APCI-) *m/z* 399.0.

Example 8:

6-[3-[2-Methoxy-5-(benzoxazole-2-yl)phenyl]-3-(methyl)ureido]hexanoic acid hydroxyamide

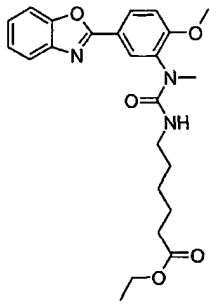
(a) 2-(3-*N*-Methylamino-4-methoxyphenyl)benzoxazole



To a stirred solution of 2-(3-amino-4-methoxyphenyl)benzoxazole (500mg, 2.08mmol) in anhydrous dimethylformamide (3ml) was added N,N-dimethylformamide dimethyl acetal (1.52ml, 11.45mmol). The reaction was stirred at 40°C for 1h. After allowing to cool to room temperature, sodium borohydride (552mg, 14.6mmol) was added and the reaction was stirred overnight. Sodium borohydride (276mg, 7.28mmol) was added and the reaction was heated at 50°C overnight. The mixture

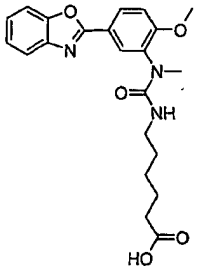
was partitioned between ethyl acetate (100ml) and saturated sodium hydrogen carbonate solution (50ml). The organic layer was washed with water (3×50ml), saturated sodium chloride solution (50ml), dried (Na_2SO_4) and concentrated. The crude compound was subjected to flash silica gel column chromatography using 1% methanol-dichloromethane as eluant to give the subtitle compound (247mg, 47%). ^{1}H NMR (DMSO): δ 2.81 (3H, d), 3.88 (3H, s), 5.44 (1H, q), 7.00 (1H, d), 7.21 (1H, d), 7.34-7.40 (2H, m), 7.47 (1H, dd), 7.72-7.77 (2H, m).

(b) 6-[3-[2-Methoxy-5-(benzoxazole-2-yl)phenyl]-3-(methyl)ureido]hexanoic acid ethyl ester



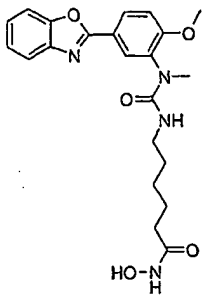
Prepared by the method of Example 2c) from 2-(3-*N*-methylamino-4-methoxyphenyl)-benzoxazole (240mg, 0.94mmol) and ethyl 6-isocyanatohexanoate (0.25ml, 1.42mmol) the subtitle compound was obtained, (186mg, 45%). ^{1}H NMR (DMSO): δ 1.12-1.24 (5H, m), 1.30-1.40 (2H, m), 1.44-1.54 (2H, m), 2.24 (2H, t), 2.95 (2H, q), 3.04 (3H, s), 3.89 (3H, s), 4.02 (2H, q), 5.95 (1H, t), 7.34 (1H, d), 7.37-7.43 (2H, m), 7.75-7.78 (2H, m), 7.94 (1H, d), 8.14 (1H, dd).

(c) 6-[3-[2-Methoxy-5-(benzoxazole-2-yl)phenyl]-3-(methyl)ureido]hexanoic acid



Prepared by the method of Example 2d) from 6-[3-[2-methoxy-5-(benzoxazole-2-yl)phenyl]-3-(methyl)ureido]hexanoic acid ethyl ester (185mg, 0.42mmol) and lithium hydroxide (50mg, 2.11mmol) the subtitle compound was obtained, (141mg, 81%). ^{1}H NMR (DMSO): δ 1.14-1.24 (2H, m), 1.30-1.40 (2H, m), 1.42-1.52 (2H, m), 2.17 (2H, t), 2.95 (2H, q), 3.04 (3H, s), 3.89 (3H, s), 5.96 (1H, t), 7.34 (1H, d), 7.36-7.43 (2H, m), 7.76-7.78 (2H, m), 7.94 (1H, d), 8.14 (1H, dd), 11.98 (1H, bs).

(d) 6-[3-[2-Methoxy-5-(benzoxazole-2-yl)phenyl]-3-(methyl)ureido]hexanoic acid hydroxyamide

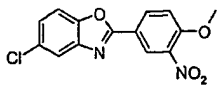


Prepared by the method of Example 2e) from 6-[3-[2-methoxy-5-(benzoxazole-2-yl)phenyl]-3-(methyl)ureido]hexanoic acid (140mg, 0.34mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (102mg, 0.58mmol), N-methylmorpholine (0.11ml, 1.02mmol) and *tert*-butyldimethylsilyl hydroxylamine. The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (2×50ml) and then stirred vigorously with 2M hydrochloric acid for 20min. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated until a precipitate formed. The solid was collected by filtration, washed with ethyl acetate and dried under vacuum to give the title compound (30mg, 21%). ^{1}H NMR (DMSO): δ 1.11-1.21 (2H, m), 1.29-1.38 (2H, m), 1.40-1.50 (2H, m), 1.91 (2H, t), 2.94 (2H, q), 3.04 (3H, s), 3.89 (3H, s), 5.95 (1H, t), 7.33 (1H, d), 7.36-7.42 (2H, m), 7.77 (2H, dd), 7.94 (1H, d), 8.14 (1H, m), 8.66 (1H, s), 10.33 (1H, s). MS (APCI+) *m/z* 427.2 MS (APCI-) *m/z* 425.5.

Example 9:

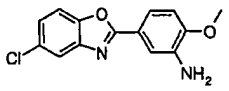
6-[3-[5-(5-Chlorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid hydroxyamide

(a) 5-Chloro-2-(4-methoxy-3-nitrophenyl)benzoxazole



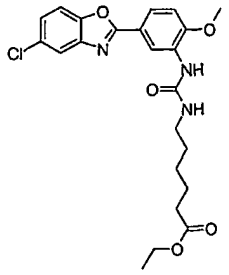
Prepared by the method of Example 2a) from 2-amino-4-chlorophenol (300mg, 2.09mmol) and 4-methoxy-3-nitrobenzoyl chloride (500mg, 2.32mmol) the subtitle compound was obtained, (275mg, 43%). ^{1}H NMR (DMSO): δ 4.00 (3H, s), 7.43 (1H, dd), 7.55 (1H, d), 7.77 (1H, d), 7.86 (1H, d), 8.36 (1H, dd), 8.55 (1H, d).

(b) 5-Chloro-2-(3-amino-4-methoxyphenyl)benzoxazole



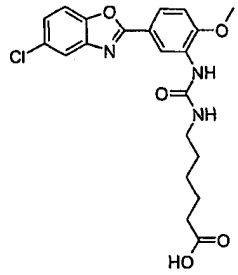
Prepared by the method of Example 2b) from 5-chloro-2-(4-methoxy-3-nitrophenyl)benzoxazole (275mg, 0.90mmol) the subtitle compound was obtained, (233mg, 94%). ^{1}H NMR (DMSO): δ 3.98 (3H, s), 5.20 (2H, s), 7.06 (1H, d), 7.47 (2H, m), 7.55 (1H, d), 7.84 (1H, d), 7.89 (1H, d).

(c) 6-[3-[5-(5-Chlorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid ethyl ester



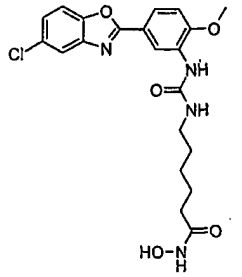
Prepared by the method of Example 2c) from 5-chloro-2-(3-amino-4-methoxyphenyl)benzoxazole (233mg, 0.85mmol) and ethyl 6-isocyanatohexanoate (0.23ml, 1.27mmol) the subtitle compound was obtained, (298mg, 76%). ^{1}H NMR (DMSO): δ 1.17 (3H, t), 1.25-1.35 (2H, m), 1.41-1.48 (2H, m), 1.50-1.60 (2H, m), 2.30 (2H, t), 3.10 (2H, q), 3.96 (3H, s), 4.05 (2H, q), 6.98 (1H, t), 7.20 (1H, d), 7.43 (1H, dd), 7.76 (1H, dd), 7.82 (1H, d), 7.86 (1H, d), 8.15 (1H, s), 9.06 (1H, s).

(d) 6-[3-[5-(5-Chlorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid



Prepared by the method of Example 2d) from 6-[3-[5-(5-chlorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid ethyl ester (282mg, 0.61mmol) and lithium hydroxide (73mg, 3.06mmol) the subtitle compound was obtained, (225mg, 85%). ^{1}H NMR (DMSO): δ 1.27-1.35 (2H, m), 1.38-1.58 (4H, m), 2.22 (2H, t), 3.10 (2H, q), 3.96 (3H, s), 6.98 (1H, t), 7.20 (1H, d), 7.32 (1H, dd), 7.76 (1H, dd), 7.81 (1H, d), 7.85 (1H, d), 8.17 (1H, s), 9.06 (1H, d), 12.00 (1H, s).

(e) 6-[3-[5-(5-Chlorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid hydroxyamide

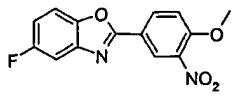


Prepared by the method of Example 2e) from 6-[3-[5-(5-chlorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid (199mg, 0.46mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (137mg, 0.78mmol), N-methylmorpholine (0.15ml, 1.38mmol) and *tert*-butyldimethylsilyl hydroxylamine (102mg, 0.69mmol) the title compound was obtained (173mg, 84%). ^{1}H NMR (DMSO): δ 1.22-1.32 (2H, m), 1.40-1.57 (4H, m), 1.96 (2H, t), 3.10 (2H, bs), 3.98 (3H, s), 7.05 (1H, bs), 7.24 (1H, d), 7.47 (1H, dd), 7.81 (1H, dd), 7.86 (1H, d), 7.91 (1H, d), 8.20 (1H, s), 9.11 (1H, s), 10.42 (1H, bs). MS (APCI+) *m/z* 447, (APCI-) *m/z* 445.

Example 10:

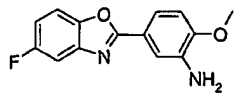
6-[3-[5-(5-Fluorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid hydroxyamide

(a) 5-Fluoro-2-(4-methoxy-3-nitrophenyl)benzoxazole



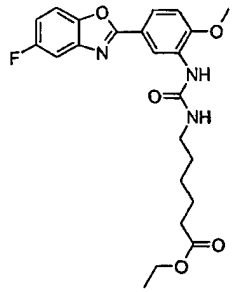
Prepared by the method of Example 2a) from 2-amino-4-fluorophenol (266mg, 2.09mmol) and 4-methoxy-3-nitrobenzoyl chloride (500mg, 2.32mmol) the subtitle compound was obtained, (386mg, 64%). ^{1}H NMR (DMSO): δ 4.01 (3H, s), 7.31 (1H, dt), 7.60 (1H, d), 7.70 (1H, dd), 7.84 (1H, dd), 8.43 (1H, dd), 8.60 (1H, d).

(b) 5-Fluoro-2-(3-amino-4-methoxyphenyl)benzoxazole



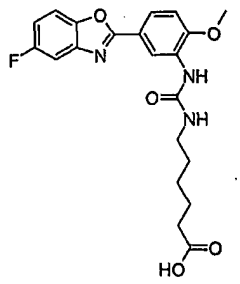
Prepared by the method of Example 2b) from 5-fluoro-2-(4-methoxy-3-nitrophenyl)benzoxazole (386mg, 1.34mmol) the subtitle compound was obtained, (297mg, 86%). ^{1}H NMR (DMSO): δ 3.80 (3H, s), 5.08 (2H, s), 6.90 (1H, d), 7.12 (1H, dt), 7.32 (1H, dd), 7.39 (1H, d), 7.50 (1H, dd), 7.67 (1H, dd).

(c) 6-[3-[5-(5-Fluorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid ethyl ester



Prepared by the method of Example 2c) from 5-fluoro-2-(3-amino-4-methoxyphenyl)benzoxazole (297mg, 1.15mmol) and ethyl 6-isocyanatohexanoate (0.31ml, 1.72mmol) the subtitle compound was obtained, (379mg, 74%). ^{1}H NMR (DMSO): δ 1.17 (3H, t), 1.25-1.35 (2H, m), 1.41-1.48 (2H, m), 1.50-1.60 (2H, m), 2.30 (2H, t), 3.10 (2H, q), 3.96 (3H, s), 4.05 (2H, q), 6.98 (1H, t), 7.20 (1H, d), 7.23 (1H, dt), 7.62 (1H, dd), 7.78 (1H, dd), 7.80 (1H, dd), 8.15 (1H, s), 9.06 (1H, s).

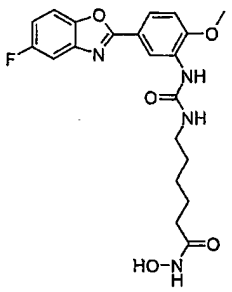
(d) 6-[3-[5-(5-Fluorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid



Prepared by the method of Example 2d) from 6-[3-[5-(5-fluorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid ethyl ester (326mg, 0.73mmol) and lithium hydroxide (88mg, 3.67mmol) the subtitle compound was obtained, (247mg, 81%). ^{1}H NMR (DMSO): δ 1.25-1.35 (2H, m),

1.38-1.58 (4H, m), 2.21 (2H, t), 3.10 (2H, q), 3.97 (3H, s), 6.98 (1H, t), 7.20 (1H, d), 7.23 (1H, dt), 7.62 (1H, dd), 7.78 (1H, dd), 7.80 (1H, dd), 8.15 (1H, s), 9.06 (1H, d), 12.01 (1H, s).

(e) 6-[3-[5-(5-Fluorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid hydroxyamide

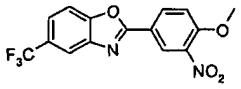


Prepared by the method of Example 2e) from 6-[3-[5-(5-fluorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid (230mg, 0.55mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (165mg, 0.94mmol), N-methylmorpholine (0.18ml, 1.66mmol) and *tert*-butyldimethylsilyl hydroxylamine (122mg, 0.83mmol) the title compound was obtained (130mg, 54%). ^{1}H NMR (DMSO): δ 1.22-1.30 (2H, m), 1.37-1.53 (4H, m), 1.94 (2H, t), 3.08 (2H, bs), 3.95 (3H, s), 6.95 (1H, t), 7.15 (1H, d), 7.22 (1H, dt), 7.60 (1H, dd), 7.72 (1H, dd), 7.77 (1H, dd), 8.10 (1H, s), 9.03 (1H, s), 10.32 (1H, bs). MS (APCI+) *m/z* 431, (APCI-) *m/z* 429.

Example 11:

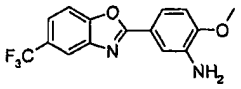
6-[3-[2-Methoxy-5-[5-(trifluoromethyl)benzoxazole-2-yl]phenyl]ureido]hexanoic acid hydroxyamide

(a) 5-Trifluoromethyl-2-(4-methoxy-3-nitrophenyl)benzoxazole



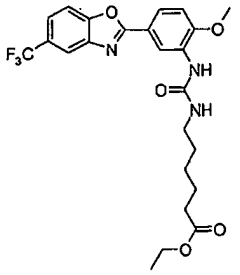
Prepared by the method of Example 2a) from 2-amino-4-(trifluoromethyl)phenol (370mg, 2.09mmol) and 4-methoxy-3-nitrobenzoyl chloride (500mg, 2.32mmol) the subtitle compound was obtained, (371mg, 52%). ^{1}H NMR (DMSO): δ 4.05 (3H, s), 7.62 (1H, d), 7.80 (1H, d), 8.02 (1H, d), 8.20 (1H, s), 8.43 (1H, dd), 8.62 (1H, s).

(b) 5-Trifluoromethyl-2-(3-amino-4-methoxyphenyl)benzoxazole



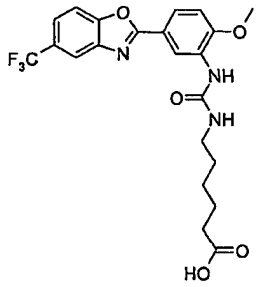
Prepared by the method of Example 2b) from 5-trifluoromethyl-2-(4-methoxy-3-nitrophenyl)-benzoxazole (370mg, 1.09mmol) the subtitle compound was obtained, (325mg, 97%). ^{1}H NMR (DMSO): δ 3.90 (3H, s), 5.20 (2H, s), 7.02 (1H, d), 7.47 (1H, dd), 7.55 (1H, d), 7.75 (1H, dd), 7.96 (1H, d), 8.15 (1H, s).

(c) 6-[3-[2-Methoxy-5-[5-(trifluoromethyl)benzoxazole-2-yl]phenyl]ureido]hexanoic acid ethyl ester



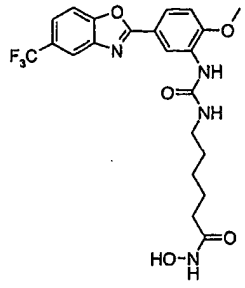
Prepared by the method of Example 2c) from 5-trifluoromethyl-2-(3-amino-4-methoxyphenyl)-benzoxazole (325mg, 1.06mmol) and ethyl 6-isocyanatohexanoate (0.28ml, 1.58mmol) the subtitle compound was obtained, (425mg, 81%). ^{1}H NMR (DMSO): δ 1.17 (3H, t), 1.25-1.35 (2H, m), 1.41-1.48 (2H, m), 1.50-1.60 (2H, m), 2.30 (2H, t), 3.10 (2H, q), 3.96 (3H, s), 4.05 (2H, q), 6.98 (1H, t), 7.20 (1H, d), 7.76 (1H, d), 7.81 (1H, dd), 8.01 (1H, d), 8.16 (1H, d), 9.10 (1H, s).

(d) 6-[3-[2-Methoxy-5-[5-(trifluoromethyl)benzoxazole-2-yl]phenyl]ureido]hexanoic acid



Prepared by the method of Example 2d) from 6-[3-[2-methoxy-5-[5-(trifluoromethyl)benzoxazole-2-yl]phenyl]ureido]hexanoic acid ethyl ester (410mg, 0.83mmol) and lithium hydroxide (99mg, 4.16mmol) the subtitle compound was obtained, (349mg, 90%). ^{1}H NMR (DMSO): δ 1.25-1.35 (2H, m), 1.38-1.58 (4H, m), 2.22 (2H, t), 3.11 (2H, q), 3.97 (3H, s), 6.98 (1H, t), 7.21 (1H, d), 7.75 (1H, dd), 7.82 (1H, dd), 8.01 (1H, d), 8.18 (1H, d), 9.10 (1H, d), 12.02 (1H, s).

(e) 6-[3-[2-Methoxy-5-[5-(trifluoromethyl)benzoxazole-2-yl]phenyl]ureido]hexanoic acid hydroxyamide



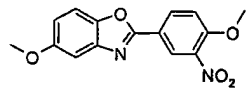
Prepared by the method of Example 2e) from 6-[3-[2-methoxy-5-[5-(trifluoromethyl)-benzoxazole-2-yl]phenyl]ureido]hexanoic acid (337mg, 0.73mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (216mg, 1.23mmol), N-methylmorpholine (0.24ml, 2.18mmol) and *tert*-butyldimethylsilyl hydroxylamine (160mg, 1.09mmol) the title compound was obtained (195mg, 56%). ^{1}H NMR (DMSO): δ 1.23-1.32 (2H, m), 1.37-1.56 (4H, m), 1.96 (2H, t), 3.10 (2H, q), 3.97 (3H, s), 6.98 (1H, t), 7.22 (1H, d),

7.77 (1H, dd), 7.80 (1H, dd), 8.01 (1H, d), 8.18 (1H, s), 8.68 (1H, s), 9.10 (1H, d), 10.36 (1H, bs). MS (APCI+) *m/z* 481, (APCI-) *m/z* 478.

Example 12:

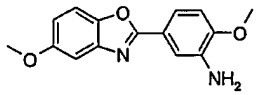
6-[3-[2-Methoxy-5-(5-methoxybenzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide

(a) 5-Methoxy-2-(4-methoxy-3-nitrophenyl)benzoxazole



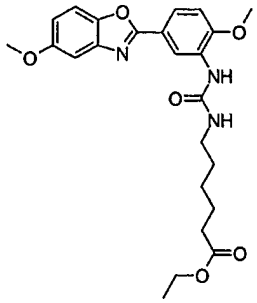
Prepared by the method of Example 2a) from 2-amino-4-methoxyphenol (291mg, 2.09mmol) and 4-methoxy-3-nitrobenzoyl chloride (500mg, 2.32mmol) the subtitle compound was obtained, (189mg, 30%). ^{1}H NMR (DMSO): δ 3.82 (3H, s), 4.05 (3H, s), 7.02 (1H, dd), 7.36 (1H, d), 7.60 (1H, d), 7.70 (1H, d), 8.40 (1H, dd), 8.58 (1H, d).

(b) 2-(3-Amino-4-methoxyphenyl)-5-methoxybenzoxazole



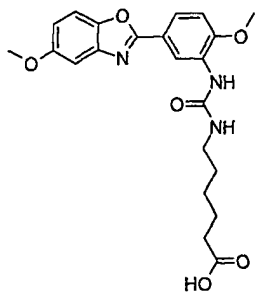
Prepared by the method of Example 2b) from 5-methoxy-2-(4-methoxy-3-nitrophenyl)benzoxazole (189mg, 0.63mmol) the subtitle compound was obtained, (148mg, 87%). ^{1}H NMR (DMSO): δ 3.85 (3H, s), 3.90 (3H, s), 5.12 (2H, s), 6.95 (1H, dd), 6.98 (1H, d), 7.28 (1H, d), 7.40 (1H, dd), 7.47 (1H, d), 7.62 (1H, d).

(c) 6-[3-[2-Methoxy-5-(5-methoxybenzoxazole-2-yl)phenyl]ureido]hexanoic acid ethyl ester



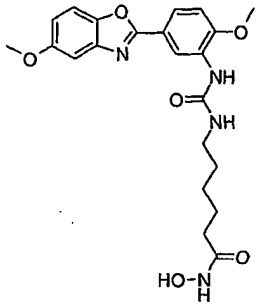
Prepared by the method of Example 2c) from 2-(3-amino-4-methoxyphenyl)-5-methoxybenzoxazole (148mg, 0.55mmol) and ethyl 6-isocyanatohexanoate (0.15ml, 0.82mmol) the subtitle compound was obtained, (48mg, 19%). ^{1}H NMR (DMSO): δ 1.17 (3H, t), 1.25-1.35 (2H, m), 1.41-1.48 (2H, m), 1.50-1.60 (2H, m), 2.30 (2H, t), 3.10 (2H, q), 3.82 (3H, s), 3.94 (3H, s), 4.05 (2H, q), 6.98 (1H, t), 7.18 (1H, d), 7.32 (1H, d), 7.65 (1H, d), 7.72 (1H, dd), 8.10 (1H, s), 9.03 (1H, d).

(d) 6-[3-[2-Methoxy-5-(5-methoxybenzoxazole-2-yl)phenyl]ureido]hexanoic acid



Prepared by the method of Example 2d) from 6-[3-[2-methoxy-5-(5-methoxybenzoxazole-2-yl)phenyl]ureido]hexanoic acid ethyl ester (42mg, 0.09mmol) and lithium hydroxide (11mg, 0.46mmol) the subtitle compound was obtained, (34mg, 85%). ^{1}H NMR (DMSO): δ 1.25-1.35 (2H, m), 1.38-1.58 (4H, m), 2.22 (2H, t), 3.10 (2H, q), 3.82 (3H, s), 3.96 (3H, s), 6.98 (1H, dd), 7.17 (1H, d), 7.31 (1H, d), 7.66 (1H, d), 7.73 (1H, dd), 8.12 (1H, s), 9.02 (1H, d), 12.02 (1H, bs).

(e) 6-[3-[2-Methoxy-5-(5-methoxybenzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide

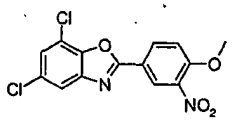


Prepared by the method of Example 2e) from 6-[3-[2-methoxy-5-(5-methoxybenzoxazole-2-yl)phenyl]ureido]hexanoic acid (23mg, 0.05mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (16.3mg, 0.09mmol), N-methylmorpholine (0.02ml, 0.16mmol) and *tert*-butyldimethylsilyl hydroxylamine (12.1mg, 0.08mmol) the title compound was obtained (16mg, 66%). ^{1}H NMR (DMSO): δ 1.23-1.32 (2H, m), 1.37-1.56 (4H, m), 1.96 (2H, t), 3.10 (2H, q), 3.82 (3H, s), 3.97 (3H, s), 6.98 (1H, dd), 7.17 (1H, d), 7.31 (1H, d), 7.65 (1H, d), 7.74 (1H, dd), 8.13 (1H, s), 9.04 (1H, s), 10.39 (1H, s). MS (APCI+) *m/z* 443, (APCI-) *m/z* 441.

Example 13:

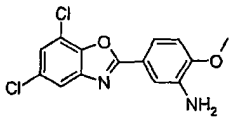
6-[3-[2-Methoxy-5-(5,7-dichlorobenzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide

(a) 5,7-Dichloro-2-(4-methoxy-3-nitrophenyl)benzoxazole



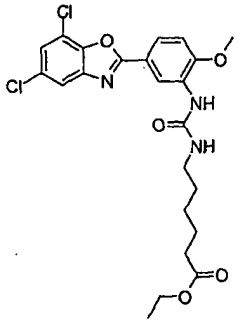
Prepared by the method of Example 2a) from 2-amino-4, 6-dichlorophenol (372mg, 2.09mmol) and 4-methoxy-3-nitrobenzoyl chloride (500mg, 2.32mmol) the subtitle compound was obtained, (376mg, 53%). ^{1}H NMR (DMSO): δ 4.05 (3H, s), 7.62 (1H, d), 7.72 (1H, d), 7.94 (1H, d), 8.42 (1H, dd), 8.61 (1H, d).

(b) 2-(3-Amino-4-methoxyphenyl)-5,7-dichlorobenzoxazole



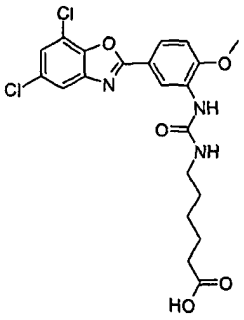
Prepared by the method of Example 2b) from 5,7-dichloro-2-(4-methoxy-3-nitrophenyl)benzoxazole (376mg, 1.11mmol) the subtitle compound was obtained, (245mg, 71%). ^{1}H NMR (DMSO): δ 3.90 (3H, s), 5.20 (2H, s), 7.02 (1H, d), 7.45 (1H, dd), 7.50 (1H, d), 7.65 (1H, d), 7.87 (1H, d).

(c) 6-[3-[2-Methoxy-5-(5,7-dichlorobenzoxazole-2-yl)phenyl]ureido]hexanoic acid ethyl ester



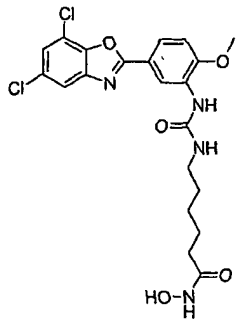
Prepared by the method of Example 2c) from 2-(3-amino-4-methoxyphenyl)-5,7-dichlorobenzoxazole (245mg, 0.79mmol) and ethyl 6-isocyanatohexanoate (0.21ml, 1.19mmol) the subtitle compound was obtained, (377mg, 97%). ^{1}H NMR (DMSO): δ 1.17 (3H, t), 1.25-1.35 (2H, m), 1.41-1.48 (2H, m), 1.50-1.61 (2H, m), 2.30 (2H, t), 3.10 (2H, q), 3.96 (3H, s), 4.05 (2H, q), 6.98 (1H, t), 7.21 (1H, d), 7.66 (1H, d), 7.77 (1H, dd), 7.88 (1H, d), 8.16 (1H, s), 9.07 (1H, s).

(d) 6-[3-[2-Methoxy-5-[5,7-dichlorobenzoxazole-2-yl]phenyl]ureido]hexanoic acid



Prepared by the method of Example 2d) from 6-[3-[2-methoxy-5-(5,7-dichlorobenzoxazole-2-yl)phenyl]ureido]hexanoic acid ethyl ester (369mg, 0.75mmol) and lithium hydroxide (89mg, 3.73mmol) the subtitle compound was obtained, (306mg, 88%). ^{1}H NMR (DMSO): δ 1.25-1.35 (2H, m), 1.38-1.58 (4H, m), 2.25 (2H, t), 3.11 (2H, q), 3.98 (3H, s), 6.98 (1H, t), 7.21 (1H, d), 7.68 (1H, d), 7.78 (1H, dd), 7.90 (1H, d), 8.18 (1H, s), 9.07 (1H, d), 12.02 (1H, s).

(e) 6-[3-[2-Methoxy-5-(5,7-dichlorobenzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide

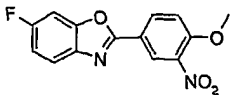


Prepared by the method of Example 2e) from 6-[3-[2-methoxy-5-(5,7-dichlorobenzoxazole-2-yl)-phenyl]ureido]hexanoic acid (289mg, 0.62mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (185mg, 1.05mmol), N-methylmorpholine (0.20ml, 1.86mmol) and *tert*-butyldimethylsilyl hydroxylamine (137mg, 0.93mmol) the title compound was obtained (201mg, 67%). ^{1}H NMR (DMSO): δ 1.23-1.32 (2H, m), 1.37-1.56 (4H, m), 1.97 (2H, t), 3.10 (2H, q), 3.97 (3H, s), 6.98 (1H, t), 7.22 (1H, d), 7.66 (1H, d), 7.77 (1H, dd), 7.89 (1H, d), 8.18 (1H, s), 8.68 (1H, bs), 9.07 (1H, s), 10.36 (1H, bs). MS (APCI+) *m/z* 481, (APCI-) *m/z* 479.

Example 14:

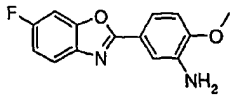
6-[3-[5-(6-Fluorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid hydroxyamide

(a) 6-Fluoro-2-(4-methoxy-3-nitrophenyl)benzoxazole



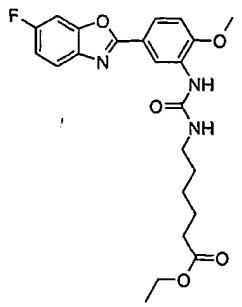
Prepared by the method of Example 2a) from 2-amino-5-fluorophenol (266mg, 2.09mmol) and 4-methoxy-3-nitrobenzoyl chloride (500mg, 2.32mmol) the subtitle compound was obtained, (486mg, 81%). ^{1}H NMR (DMSO): δ 4.05 (3H, s), 7.32 (1H, dt), 7.62 (1H, d), 7.79-7.87 (2H, m), 8.41 (1H, dd), 8.59 (1H, d).

(b) 2-(3-Amino-4-methoxyphenyl)-6-fluorobenzoxazole



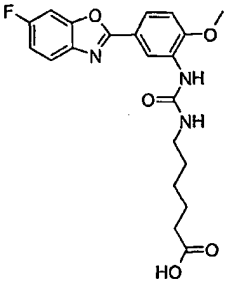
Prepared by the method of Example 2b) from 6-fluoro-2-(4-methoxy-3-nitrophenyl)benzoxazole (486mg, 1.69mmol) the subtitle compound was obtained, (352mg, 81%). ^{1}H NMR (DMSO): δ 3.89 (3H, s), 5.12 (2H, s), 7.00 (1H, d), 7.24 (1H, m), 7.39 (1H, dd), 7.47 (1H, d), 7.74 (2H, m).

(c) 6-[3-[5-(6-Fluorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid ethyl ester



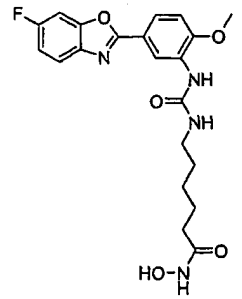
Prepared by the method of Example 2c) from 2-(3-amino-4-methoxyphenyl)-6-fluorobenzoxazole (352mg, 1.37mmol) and ethyl 6-isocyanatohexanoate (0.37ml, 2.06mmol) the subtitle compound was obtained, (452mg, 74%). ^{1}H NMR (DMSO): δ 1.17 (3H, t), 1.25-1.35 (2H, m), 1.40-1.48 (2H, m), 1.50-1.61 (2H, m), 2.30 (2H, t), 3.10 (2H, q), 3.94 (3H, s), 4.05 (2H, q), 6.98 (1H, t), 7.19 (1H, d), 7.26 (1H, m), 7.76 (3H, m), 8.13 (1H, s), 9.04 (1H, s).

(d) 6-[3-[5-(6-Fluorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid



Prepared by the method of Example 2d) from 6-[3-[5-(6-fluorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid ethylester (447mg, 1.01mmol) and lithium hydroxide (121mg, 5.03mmol) the subtitle compound was obtained, (340mg, 81%). ^{1}H NMR (DMSO): δ 1.25-1.35 (2H, m), 1.38-1.58 (4H, m), 2.22 (2H, t), 3.11 (2H, q), 3.96 (3H, s), 6.98 (1H, t), 7.19 (1H, d), 7.27 (2H, m), 7.76 (3H, m), 8.16 (1H, s), 9.04 (1H, d), 12.02 (1H, s).

(e) 6-[3-[5-(6-Fluorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid hydroxyamide

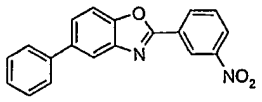


Prepared by the method of Example 2e) from 6-[3-[5-(6-fluorobenzoxazole-2-yl)-2-methoxyphenyl]ureido]hexanoic acid (316mg, 0.76mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (227mg, 1.29mmol), N-methyl morpholine (0.25ml, 2.28mmol) and *tert*-butyl dimethylsilyl hydroxylamine (168mg, 1.14mmol) the title compound was obtained (250mg, 76%). ^{1}H NMR (DMSO): δ 1.23-1.32 (2H, m), 1.37-1.56 (4H, m), 1.97 (2H, t), 3.10 (2H, bs), 3.96 (3H, s), 6.98 (1H, t), 7.18 (1H, d), 7.26 (2H, m), 7.76 (3H, m), 8.14 (1H, s), 9.04 (1H, s), 10.37 (1H, bs). MS (APCI+) *m/z* 431, (APCI-) *m/z* 430.

Example 15:

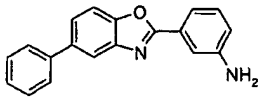
6-[3-[3-(5-Phenylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide

(a) 2-(3-Nitrophenyl)-5-phenylbenzoxazole



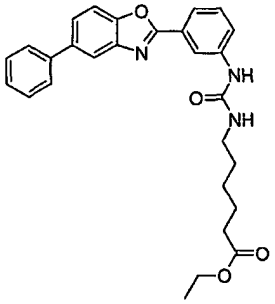
Prepared by the method of Example 2a) from 2-amino-4-phenylphenol (5.00g, 26.99mmol) and 3-nitrobenzoyl chloride (5.00g, 26.99mmol) the subtitle compound was obtained, (7.90g, 93%). ^{1}H NMR (DMSO): δ 7.42 (1H, q), 7.52 (2H, t), 7.78 (3H, m), 7.93 (2H, m), 8.12 (1H, s), 8.49 (1H, d), 8.63 (1H, d), 8.89 (1H, s).

(b) 2-(3-Aminophenyl)-5-phenylbenzoxazole



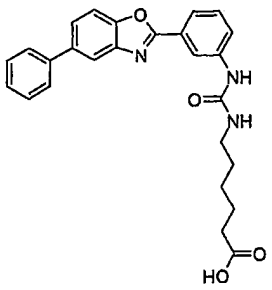
Prepared by the method of Example 2b) from 2-(3-nitrophenyl)-5-phenylbenzoxazole (7.90g, 24.97mmol) the subtitle compound was obtained, (6.36g, 89%). ^{1}H NMR (DMSO): δ 5.51 (2H, s), 6.81 (1H, d), 7.25 (1H, t), 7.38 (2H, m), 7.49 (3H, m), 7.72 (3H, m), 7.85 (1H, d), 8.04 (1H, d).

(c) 6-[3-[3-(5-Phenylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid ethyl ester



Prepared by the method of Example 2c) from 2-(3-aminophenyl)-5-phenylbenzoxazole (500mg, 1.75mmol) and ethyl 6-isocyanatohexanoate (0.47ml, 2.62mmol) the subtitle compound was obtained, (670mg, 82%). ^{1}H NMR (DMSO): δ 1.17 (3H, t), 1.25-1.35 (2H, m), 1.38-1.58 (4H, m), 2.30 (2H, t), 3.10 (2H, q), 4.05 (2H, q), 6.25 (1H, t), 7.36-7.56 (5H, m), 7.71-7.78 (4H, m), 7.88 (1H, d), 8.07 (1H, s), 8.52 (1H, s), 8.80 (1H, s).

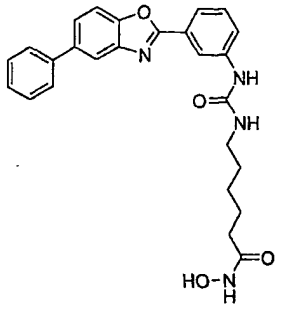
(d) 6-[3-[3-(5-Phenylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid



Prepared by the method of Example 2d) from 6-[3-[3-(5-phenylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid ethyl ester (670mg, 1.42mmol) and lithium hydroxide (170mg,

7.10mmol) the subtitle compound was obtained, (570mg, 90%). ^{1}H NMR (DMSO): δ 1.25-1.35 (2H, m), 1.38-1.58 (4H, m), 2.22 (2H, t), 3.11 (2H, q), 6.25 (1H, t), 7.37-7.55 (5H, m), 7.70-7.78 (4H, m), 7.89 (1H, d), 8.08 (1H, s), 8.52 (1H, s), 8.80 (1H, s), 12.03 (1H, s).

(e) 6-[3-[3-(5-Phenylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid hydroxyamide



Prepared by the method of Example 2e) from 6-[3-[3-(5-phenylbenzoxazole-2-yl)phenyl]ureido]hexanoic acid (500mg, 1.13mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (337mg, 1.92mmol), N-methyl morpholine (0.37ml, 3.38mmol) and *tert*-butyl dimethylsilyl hydroxylamine (249mg, 1.69mmol) the title compound was obtained (120mg, 23%). ^{1}H NMR (DMSO): δ 1.25-1.35 (2H, m), 1.38-1.57 (4H, m), 1.97 (2H, t), 3.10 (2H, q), 6.24 (1H, t), 7.37-7.57 (5H, m), 7.70-7.78 (4H, m), 7.88 (1H, d), 8.07 (1H, s), 8.52 (1H, s), 8.68 (1H, s), 8.81 (1H, s), 10.36 (1H, s). MS (APCI+) *m/z* 459, (APCI-) *m/z* 457.

Biological Data

Histone Deacetylase assay

A histone deacetylase assay kit was purchased from BIOMOL® Research Laboratories, AK-500, and the manufacturers protocol was followed.

The assay is based upon a substrate, which has an acetylated lysine chain. Deacetylation of the substrate, by histone deacetylase enzyme, sensitises the substrate to the developer producing a fluorophore that can be measured in a fluorometric plate reader.

The assays were performed according to the BIOMOL® protocol and the source of the histone deacetylases was HeLa nuclear extract. Components added to the wells were as follows, assay buffer (final assay volume 50µl), inhibitors (10µl), histone deacetylase source (HeLa extract, 15µl containing ~4µg), substrate (25µl, 1/200 dilution stock). The wells were mixed and the assay incubated for 30 min at R.T. before taking readings using a Victor2 fluorometric plate reader (excitation at 350nM and emission detected at 440nm).

The following table gives the histone deacetylase activity of representative compounds of the invention.

Compound	Inhibition of Histone Deacetylase (IC_{50}, nM)
Example 1	400
Example 2	12
Example 3	8
Example 4	8
Example 5	12

Example 6	19
Example 7	9
Example 9	146
Example 10	15
Example 13	128
Example 14	18

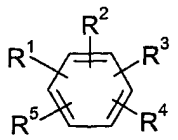
Cell Cycle Analysis and Acetylation of Histones

The compound of Example 1 was assessed for its effect on cancerous cell growth. Cell cycle analysis was performed on HL60 (human promyelocytic leukaemia cell line) cells by using BrdU incorporation and flow cytometry, methods that are well known to those skilled in the art. The compound of Example 1 was found to cause a dose dependant accumulation of cells in the G2M phase of the cell cycle, thus arresting the cells prior to mitosis.

Acetylation of histones by the compound of Example 1 was investigated using the methods described in Richon et al., (2000), PNAS, vol 98, No 18. This method is based on assessment of acetylated histone protein using a rabbit anti-acetylated histone H4 antibody and Western Blotting techniques, methods that are well known to those skilled in the art. The compound of Example 1 was found to cause a dose dependant increase in histone acetylation in MCF7 (human mammary epithelial cell line) cells.

CLAIMS:

1. A compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof:



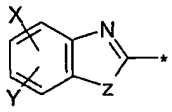
(I)

wherein

R^1, R^2 and R^3 are independently, hydrogen, halogen, CF_3, OR^6, NR^7R^8, NR^8COR^{10}, $NR^8SO_2R^{10}$ or C_{1-6} alkyl optionally substituted by hydroxyl or C_{1-6} alkoxy;

R^4 is $NR^8CONR^8R^9$;

R^5 is



wherein one of X and Y is R^{11} and the other is hydrogen or halogen; or X and Y together with the carbon atoms to which they are attached form a fused six-membered aromatic ring; Z is NR^8, O or S;

R^6 is hydrogen or C_{1-6} alkyl, C_{3-6} alkenyl or C_{3-6} alkynyl any of which can optionally be substituted by hydroxyl, C_{1-6} alkoxy or NR^7R^8;

R^7 is hydrogen or C_{1-6} alkyl or C_{3-6} alkenyl either of which can optionally be substituted by C_{1-6} alkoxy;

R^8 is hydrogen or C_{1-6} alkyl;

or the groups R^7 and R^8 may together with the nitrogen to which they are attached form a 5- or 6-membered ring which optionally contains up to two further heteroatoms selected from NR^8, S and O;

R^9 is C_{1-10} alkyl or C_{3-10} alkenyl wherein a $-CH_2-$ group other than that adjacent to the N may be replaced by -O- and wherein the alkyl or alkenyl is substituted by one or more hydroxamic acid groups (CONHOH);

or in R^4 the groups R^8 and R^9 may together with the nitrogen to which they are attached form a 5- or 6-membered ring, which is substituted with one or more hydroxamic acid groups (CONHOH);

R^{10} is C_{1-6} alkyl; and

R^{11} is hydrogen, halogen, C_{1-6} alkyl, CF_3, OCF_3, CN, OR^6 or phenyl optionally substituted by one or more substituents selected from halogen, C_{1-6} alkyl, CF_3, OCF_3, OR^6, CN and methylenedioxo; or a 5- to 10-membered heteroaryl group containing up to three heteroatoms selected from O, N and S, which heteroaryl group may optionally be substituted by one or more substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy and halogen.

2. A compound according to claim 1 where R^1, R^2 and R^3 are independently, hydrogen, halogen, OR^6, NR^7R^8, or C_{1-6} alkyl optionally substituted by hydroxyl or C_{1-6} alkoxy.

3. A compound according to any one of the preceding claims where Z is O.

4. A compound according to any one of the preceding claims where R^6 is hydrogen or C_{1-6} alkyl, C_{3-6} alkenyl or C_{3-6} alkynyl any of which can optionally be substituted by hydroxyl or C_{1-6} alkoxy.

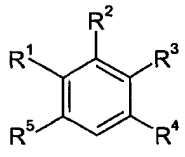
5. A compound according to any one of the preceding claims where R^{11} is hydrogen, halogen, C_{1-6} alkyl, CF_3, OCF_3, CN, OR^6 or phenyl.

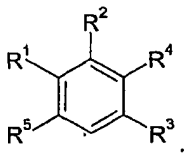
6. A compound according to any one of the preceding claims where R^1 is hydrogen, OR^6 or NR^7R^8.

7. A compound according to any one of the preceding claims where R^2 is hydrogen.

8. A compound according to any one of the preceding claims where R^3 is hydrogen, halogen or OR^6.

9. A compound according to any one of the preceding claims where the configuration of the R groups is:



or


10. A compound of formula (I) as described in any one of Examples 1 to 15 or a pharmaceutically acceptable salt or prodrug thereof.

11. A compound as defined in any one of claims 1 to 10 for use in medicine.

12. A pharmaceutical composition comprising a compound according to any one of claims 1 to 10 together with a pharmaceutically acceptable carrier or excipient.

13. The use of a compound as defined in any one of claims 1 to 10 in the manufacture of a medicament for the inhibition of histone deacetylase enzyme activity.

14. The use of a compound as defined in any one of claims 1 to 10 in the manufacture of a medicament for the treatment of a subject with cancer.

15. The use of a compound as defined in any one of claims 1 to 10, in the manufacture of a medicament for the treatment of a disease selected from angiogenesis or an angiogenesis dependent disease, an inflammatory disease and a proliferative skin disorder.

16. A compound as defined in any one of claims 1 to 10, wherein the one or more hydroxamic acid groups (CONHOH) are replaced by CONHOP wherein P is a protecting group.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 August 2004 (12.08.2004)

PCT

(10) International Publication Number
WO 2004/067480 A3

(51) International Patent Classification[7]: C07D 263/56, A61K 31/423, A61P 35/00

(21) International Application Number: PCT/GB2004/000238

(22) International Filing Date: 22 January 2004 (22.01.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0301872.8	25 January 2003 (25.01.2003)	GB
0324655.0	22 October 2003 (22.10.2003)	GB

(71) Applicant *(for all designated States except US)*: **OXFORD GLYCOSCIENCES (UK) LTD** [GB/GB]; The Forum, 86 Milton Park, Abingdon, Oxfordshire OX14 4RY (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **SCOPES, David, Ian, Carter** [GB/GB]; The Forum, 86 Milton Park, Abingdon, Oxfordshire OX14 4RY (GB).

(74) Agent: **THOMPSON, John**; c/o Celltech R & d Ltd, 208 Bath Road, Slough, Berkshire SL1 3WE (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 4 November 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED PHENYLUREA DERIVATIVES AS HDAC INHIBITORS

(57) Abstract: A series of phenylurea derivatives, further substituted on the phenyl ring by a benzoxazole, benzothiazole or benzimidazole moiety, being inhibitors of histone deacetylase, are accordingly of use in medicine, in particular for the treatment of cancer.

WO 2004/067480 A3

INTERNATIONAL SEARCH REPORT

Int onal Application No
P.../GB2004/000238

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D263/56 A61K31/423 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	MILLER T A: "Patent status of histone deacetylase inhibitors" EXPERT OPINION ON THERAPEUTIC PATENTS 2004 UNITED KINGDOM, vol. 14, no. 6, 2004, pages 791-804, XP002294154 ISSN: 1354-3776 the whole document ----- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 2004	10/09/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Kollmannsberger, M

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/GB2004/000238

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FINNIN M S ET AL: "Structures of a histone deacetylase homologue bound to the TSA and SAHA inhibitors" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 401, no. 6749, 9 September 1999 (1999-09-09), pages 188-193, XP002266214 ISSN: 0028-0836 figure 1	1-16
A	WO 02/36580 A (BONHAM LYNN ; KLEIN J PETER (US); LEUNG DAVID W (US); TANG NORINA M (U) 10 May 2002 (2002-05-10) claim 25 page 28; compound 32021	1-16
A	WO 02/085883 A (HOFFMANN LA ROCHE) 31 October 2002 (2002-10-31) claims	1-16

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/000238

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0236580 A	10-05-2002	AU 1664902 A	15-05-2002
		WO 0236580 A2	10-05-2002
		US 2002107269 A1	08-08-2002
WO 02085883 A	31-10-2002	BR 0209064 A	10-08-2004
		CA 2442994 A1	31-10-2002
		WO 02085883 A1	31-10-2002
		EP 1385837 A1	04-02-2004
		US 2002183513 A1	05-12-2002